Achalasia cardia – An observational study on histopathological, ultrastructural, manometric features and analysis of short term surgical outcomes after laparoscopic Heller's myotomy

A dissertation submitted in partial fulfilment of M.S (Branch I), General Surgery examination of Tamil Nadu Dr. M.G.R. Medical University, to be held on October 2015

DEPARTMENT OF GENERAL SURGERY

Christian Medical College, Vellore

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Abstract

Background: Achalasia cardia is a motility disorder affecting the esophagus with loss of progressive peristalsis and deglutitive relaxation of the lower esophageal sphincter. The pathogenesis of the disease and its etiology is poorly understood. Laparoscopic Heller's myotomy, pneumatic balloon dilatation of the lower esophageal sphincter and intra-esophageal injection of botulinum toxin are some of the treatment modalities available.

Type of study: Prospective observational study

Methodology: Twenty one patients who underwent laparoscopic Heller's myotomy were recruited for the study. Biopsy of the lower esophageal muscle was obtained and histopathological, immunohistochemical and ultrastructural analysis was performed. It was correlated with the clinical features, manometric features and post-operative outcomes**.**

Conclusion: Achalasia cardia is an inflammatory disease of the myentric plexus with early onset of fibrosis and progressive neuronal degeneration affecting myelinated and non-myelinated neurons. Degree of fibrosis increases with the duration of illness. Degree of fibrosis of the lower esophageal sphincter or degree of inflammation in the myentric plexus did not affect the manometric features of dysphagia or post-operative outcomes. Selective inhibition of the inhibitory neurons and inciting factors are the facets of the disease which still remains an enigma.

Contents

Introduction

Achalasia cardia is an inflammatory disease of unknown etiology which is characterised by failure of relaxation of the lower oesophageal sphincter and absence of progressive peristalsis in the lower oesophagus. These patients classically present with dysphagia to liquids more than to solids.

There have been many theories regarding the etiology of the disease and the pathophysiology of the disease is poorly understood. There are various treatment options available of the disease such as balloon dilatation, Heller's myotomy and botulinum toxin injection. Treatment with calcium channel blockers are also been tried.

Relevance of the study:

In view of the poor understanding of the pathophysiology of the disease and paucity of data in our country regarding the disease process and the clinical profile and outcomes of these patients, this observational study was performed looking at the histopathological, ultra structural, manometric features and to analyse the short term surgical outcomes after laparoscopic Heller's myotomy.

Aims and objectives

Primary objective:

- To study the histopathological , immunohistochemical and electron microscopic features of the esophageal muscle layer in achalasia cardia

Secondary objective:

- To assess the short term results after laparoscopic Heller’s myotomy procedure
- To study the correlation between the histological features and the clinical symptoms, duration and severity of symptoms and symptom relief after myotomy.

Literature review

Achalasia cardia is a esophageal motility disorder which is characterised by failure of relaxation of the lower oesophageal sphincter and absence of progressive peristalsis. This disease is a unique motility disorder with specific anatomical, functional and pathological characteristics. With recent advances, the understanding of the symptom complex of this disease can be well understood and categorised. However, the pathophysiology and the etiological factors affecting this disease still remains an enigma.

Epidemiology:

The incidence and prevalence of achalasia is 1.63/100,000 and 10.82/100,000 in a Canadian based study(1). Incidence and prevalence in the United Kingdom was 0.5/100,000 and 8/100,000(2). Men and women are equally affected. It is common between the ages and 25 and 60 years but can be seen at any age. There is no Indian data available for incidence and prevalence of this disease. In a Lucknow based study on the spectrum of causes for motor dysphagia, 77% of the subjects were diagnosed to have achalasia(3).

Classification:

Achalasia is a primary motor disorder of the oesophagus and it can be classified as primary or idiopathic if the etiology is unknown and secondary if it is a part of the symptom complex of diseases like sarcoidosis, dermatomyositis, amyloidosis, Chaga's disease and cancer in the gastro-esophageal junction. Pseudoachalsia is the

term used to when it associated with pancreatic pseudocyst around the distal esophagus. Features of gastro-esophageal junction narrowing and proximal dilation is seen in barium swallow but the manometric features are not diagnostic of achalasia.(4)

Symptoms:

The most common symptom of achalasia is dysphagia. It is more to liquids in the initial stages of the disease. Dysphagia improves sometimes with valsalva manoeuvre. Regurgitation occurs as there is usually a large volume of retained food and saliva. It is precipitated by recumbent position and it can be complicated by aspiration pneumonia. Chest pain in another infrequent symptom associated with achalasia. It can mimic ischemic heart disease. Heart burn like symptoms is also noticed and this symptom need to be differentiated from GERD as gastro-esophageal reflux rules out achalasia. One possible explanation of heart-burn like symptom could be due formation of lactic acid secondary to fermentation of the retained food particles in the lumen(4). Weight loss is usually modest and if it is pronounced, there should be a high index of suspicion for a malignancy of the gastro-esophageal junction causing secondary achalasia.

For assessment of symptom complex following therapeutic intervention, different scoring systems are formulated. Mellows and Pinkas scoring system(5) and Eckardt scoring systems(6) were commonly used.

Table 1 : Mellows and Pinkas score

score	Dysphagia
0	Able to eat normal diet
1	Able to swallow some solids
2	Able to swallow only semi solids
3	Able to swallow only liquids
4	Unable to swallow anything

Table 2 : Ekardt score

Score	Weight loss	Dysphagia	Retrosternal pain	Regurgitation
0	None	None	None	None
1	< 5 kg	Occasional	Occasional	Occasional
2	5 – 10 kg	Daily	Daily	Daily
3	>10 kg	Each meal	Each meal	Each meal

Understanding the pathophysiology of achalasia

Achalasia cardia is a primary motility disorder affecting the lower esophagus. The hallmark of this disease is loss of deglutitive relaxation of the lower esophageal sphincter and absence of progressive peristalsis.

The pathophysiology of this disease has been an area of research for long. Ironically, even with advances in science and technology this disease is still poorly understood. This can be further studied under the following headings.

- Anatomy of esophagus and lower esophageal sphincter musculature
- Enteric nervous system
- Peristalsis of esophagus
- Interstitial cells of Cajal
- Histological features of achalasia
- Etiology of achalasia

Anatomy of esophagus and lower esophageal sphincter musculature :

Esophagus is a muscular tube extending from the pharyngoesophageal junction to the esophago-gastric junction. It approximately 20cm in length and it can be anatomically divided into cervical, thoracic and abdominal esophagus. It walls is made up of four layers, mucosa, submucosa, muscularis propria and adventitia. Unlike other parts of the gut, esophagus is devoid of serosa. The muscularis propria comprises an outer circular layer and an inner longitudinal layer. The longitudinal fibres are arranged in three fasciculi, one ventral and two laterals. The three fasciculi combine as they

descend down to form the outer coat of the muscular layer. The inner circular layer is a continuation of the inferior constrictor muscle fibres and they run transversely in the upper part and obliquely in the lower esophagus. The circular layer in thicker than the longitudinal layer and it subsequently becomes a lower esophageal sphincter at the level of the gastroesophageal junction. The upper third of the esophagus is derived from the mesenchyme of the foregut and it of striated muscle fibres. The middle third is of a mixture of striated and smooth muscles and the lower third is comprised of smooth muscle.

Lower esophageal sphincter is basically a modulation of the inner circular layer. It is basically a functional unit with intrinsic and extrinsic components. The intrinsic component is a modification of the esophageal musculature and the extrinsic component is the diaphragmatic crura. It was first described by Liebermann-Meffert et al that some of the fibres at the level of the gastroesophageal junction gets modified to semi-circular which are arranged obliquely(7). They noticed two distinctive types of fibres, the sling fibres which run obliquely draping the cardia of the stomach at the greater curvature and the clasp fibres, arranged in the lesser curvature, with both ends of the fibres clasping and pulling both ends of the sling fibres. This is further confirmed with simultaneous measurement of endoscopic ultrasound and manometer and contributions of the individual components of the lower esophageal sphincter(8). Thus the clasp and sling fibres, the diaphragmatic crura and the lower circular smooth muscle are the chief contributors to the high pressure of the lower esophageal sphincter(8,9).

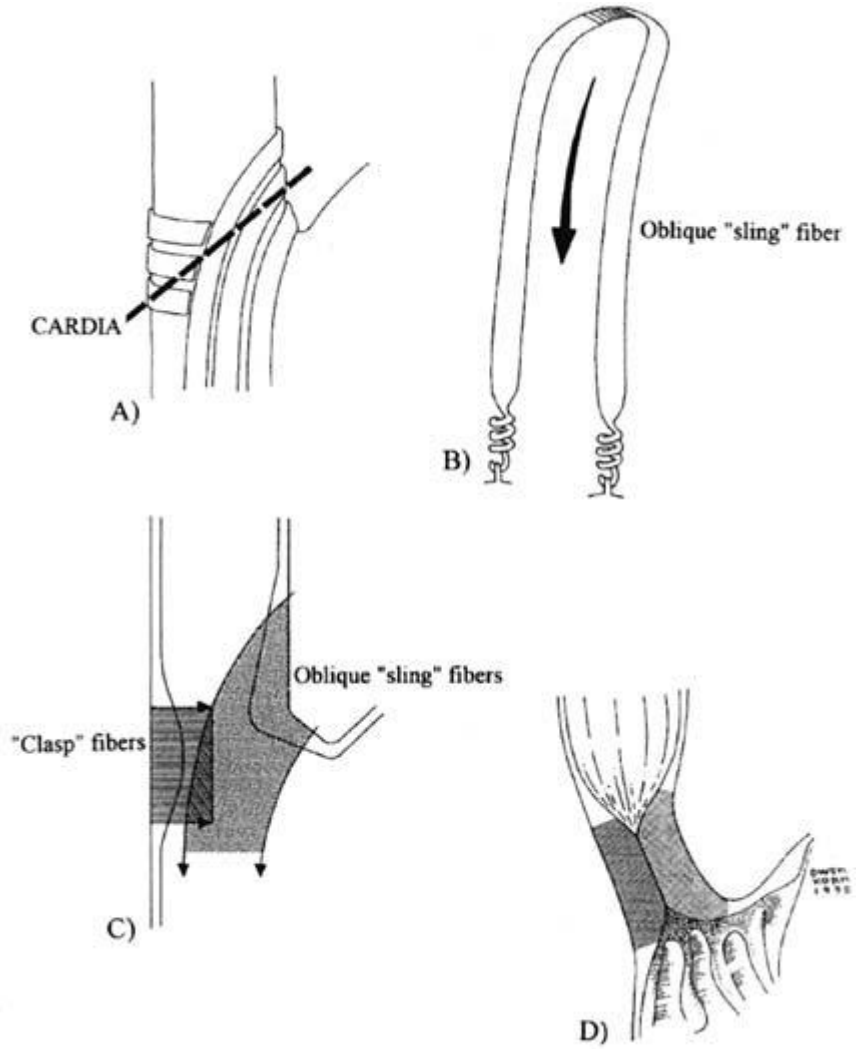


Figure 7:sling and clasp fibres (courtesy - Liebermann-Meffert;Gastroenterology 1979)

Nervous system of the lower esophagus:

To study the nervous system of the esophagus, it is essential to understand its embryological origin. Esophagus is derivative of foregut and is initially develop as a small diverticulum, called the tracheobronchial diverticulum. By 4 weeks of gestation, the neural crest cells migrate the foregut cranio-caudally. At 6 weeks of gestation, smooth muscles differentiation begins and the neural cells subsequently develop and by 7 weeks of gestation, the myentric plexus is formed. Then the neural crest cells begin to centripetal migration through the circular muscle layer resulting in the formation of sub-mucosal plexus. By 14 weeks of gestation, another network of neuronal cells forms a network surrounding the myentric plexus which is known as the interstitial cells of Cajal. They are also called gut- pacemaker cells as they are observed to have a key role in the neural transmissions within the gut(10,11).

The upper third of the esophagus is comprises of striated muscle and they are derived from the 4^{th},5^{th} and 6^{th} branchial arches and consequently they are supplied by the vagus. The lower third of the esophagus has a complex neural circuits and the embryological origin of the lower esophageal sphincter is still not clear.

Sensory innervation of the esophagus is by the sympathetic and the parasympathetic and motor innervation is primarily the parasympathetic i.e. the vagal nerve. The vagal nerve afferents mechano-sensitive and conduct stimuli such as pressure and tension and transduce them to pain sensations. The sympathetic (spinal) afferents are situated in the epithelium and they are chemo-sensitive. They conduct

stimuli from luminal acid and transduce them to pain sensations. In achalasia, there is decreased sensation to distension and acid sensation thus proving that they have decreased chemo-sensitivity and mechano-sensitivity(12). This should mean that these patients should have less pain, but chest pain is one of the well documented symptoms of achalasia. In one proposed theory, the tertiary esophageal contractions is the reason behind pain. Other possible reasons could be chronic irritation of the mucosa by retained food particles or fungal/bacterial overgrowth resulting in inflammation.

The motor supply of the esophagus is primarily by the vagus nerve. The impulses originate from nucleus ambiguous and dorsal motor nucleus. They interact with the ganglion cells in the myentric plexus of Auerbach. These ganglion serve as interneurons between the vagus and the smooth muscle(13).

Peristalsis of the esophagus :

Esophagus is a muscular tube connecting the pharynx to the stomach. It basically serves as a transit for food bolus. Swallowing is an intricately co-ordinated reflex action of the muscles of the pharynx and the neck. Various phases of deglutition include the oral phase, pharyngeal phase, esophageal phase. Initiation of swallowing reflux result in relaxation of the upper esophageal sphincter. Almost immediately after the food transits the upper esophageal sphincter, it closes to prevent retrograde motion of the food. The food bolus pushed down the esophagus by smooth peristaltic

wave staring from the pharynx till it is emptied into the stomach. There are three types of peristalsis.

- **Primary peristalsis:** Peristaltic wave is generated in response to food. The rate of the peristaltic wave is 4cm per second and it takes about 10 to 15 seconds for completion of one peristaltic wave. The strength of contraction is highest in the lower esophagus corresponding to the smooth muscles and lowest in the transition zone corresponding to the mixture of smooth and striated muscle fibres. This phase is carried on by two important process. Peristaltic wave aborally and relaxation of the lower esophageal sphincter.
- **Secondary peristalsis:** Usually there is no residual food in the esophagus following a primary peristalsis. But if there be any residual food particles following an ineffective peristalsis, it is cleared up by the secondary peristalsis. Unlike primary peristalsis, only the segment of esophagus distal to the residual food in involved and there is no relaxation of the upper esophageal sphincter.
- **Tertiary contractions:** This used to refer to the non- peristaltic contractions noted in barium study. This terminology is no longer in use.

Mechanism of esophageal contraction :

Central control of peristalsis :

As seen earlier, the esophagus is innervated by the parasympathetic and the sympathetic nerves. The parasympathetic control is by the vagal nerve fibres which originate from the Dorsal Motor Nucleus (DMN). These are myelinated pre-ganglionic fibres contained with acetylcholine neurotransmitter. There fibres synapse

with the neurons in the myentric plexus of Auerbach. The current understanding is that these neurons make direct contact with smooth muscle cells through the motor end plate. Excitatory and inhibitory function is based on the neurotransmitter produced at the nerve terminal. Nitric Oxide (NO) and Vasoactive Intestinal Peptide (VIP) are inhibitory neurotransmitters. Acetylcholine (Ach) and Substance P(SP) are excitatory

neurotransmitter (14).

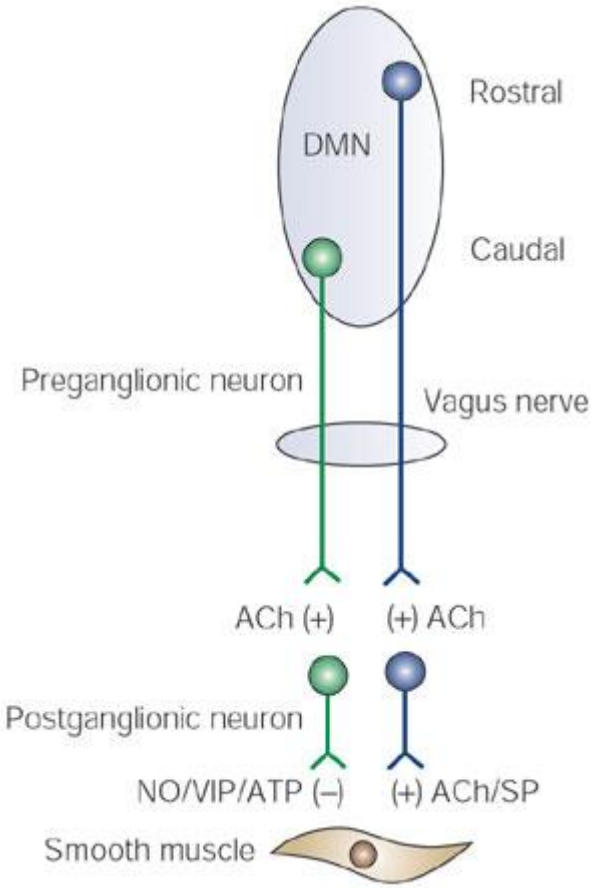


Figure 8 : Motor innervation of the esophagus (courtesy – Nature : GI motility)

The striated muscle peristalsis is less complex as the central nervous system initiates and regulates the peristaltic wave with sequential firing of impulses. It is regulated by the Swallowing Generator Program(SPG)(14).

Peripheral control of peristalsis :

The smooth muscle segment of the esophagus with its sophisticated enteric neural system can regulate a smooth peristaltic wave by itself without the regulation of the central nervous system(15). It can also initiate a peristaltic wave secondary to local distension.

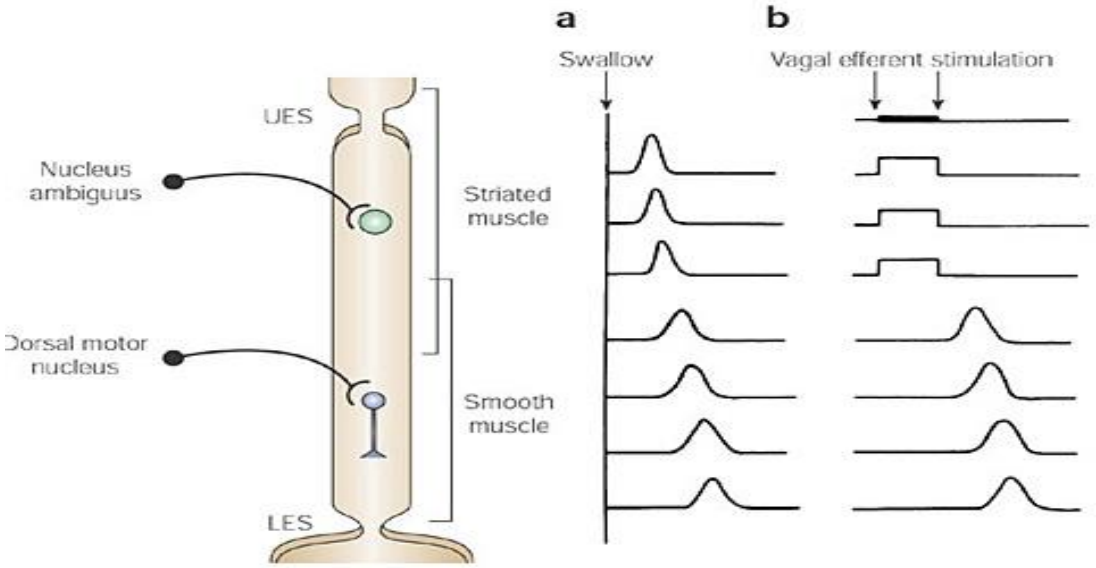


Figure 9 : Latency gradient of contraction (Courtesy – Nature : GI motility)

As the peristaltic wave passes the striated muscle and reach the smooth muscles segment the peristaltic wave is induced unlike in the striated muscle segment. A period of latency can be noted as duration between the stimulus and onset of contraction progressively increases aborally. This is called ‘latency gradient’ of

contraction. It is proven that there is an initial inhibitory wave conducted distally prior to the peristaltic wave. Thus the smooth muscle cells are initially hyperpolarised. There is difference in the duration of depolarisation and this duration progressively increases aborally(16,17). This difference could theoretically explain the delay in the onset of contraction as seen in the figure. However animal studies done based on this theory has proven that the peristalsis is vivo is much slower than the theoretical calculations. Thus, must be a mechanism other than the intrinsic latency gradient to explain this phenomenon. Another proposal is that a secondary inhibitory wave precedes depolarisation and it is regulated by intramural descending inhibitory pathways (15). In animal models it had been proven that this descending reflex is mediated by nitric oxide(18).

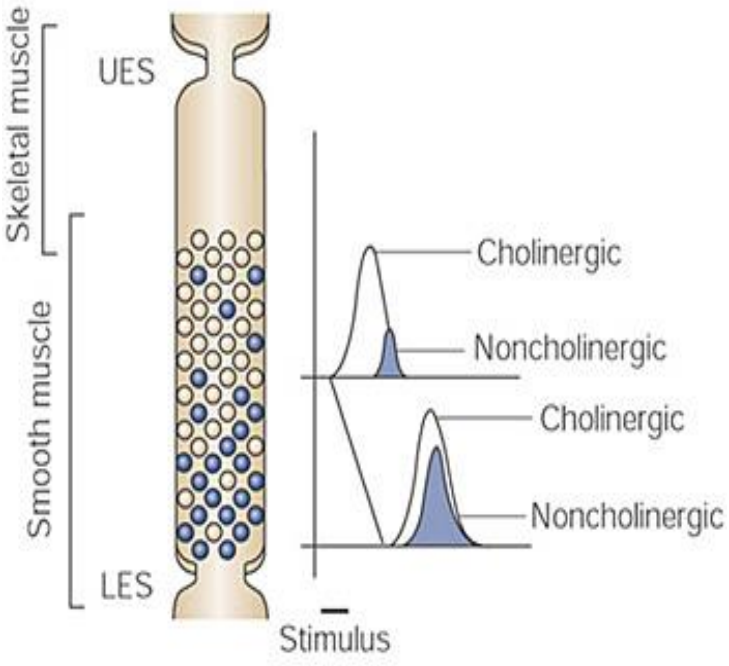


Figure 10 : Distribution of cholinergic and Non- cholinergic fibres (courtesy – Crist et al. PNAS 1984)

Another feature explaining this latency period is the unequal distribution of cholinergic and the nitriergic nerve fibres in the esophagus. The cholinergic innervation is predominant in the upper esophagus but its gradient gradually decreases in the lower esophagus and vice versa for nitriergic fibres(14)

In achalasia, there is absence of progressive peristalsis. It is clear that progressive peristalsis is a complex process which is tightly regulated by the enteric nervous system and the primary defect in achalasia is attributed to loss of inhibitory neurons.

Degluttive inhibition of peristalsis:

When the bolus of food enters the esophagus at intervals more than 10 seconds, then it can respond to one-on-one basis with relaxation of lower esophageal sphincter and then propulsion of the food bolus to the stomach. However, in reality, the food bolus enters at a rate faster than 10 seconds (eg. Drinking water in rapid succession). In such instances the phenomenon of deglutitive inhibition comes to play. Once the esophagus senses multiple food boluses entering at rapid succession, it halts all contraction and the esophagus becomes aperistaltic transiently to accommodate the incoming food bolus. During this time period, the lower esophageal sphincter remains open. After the entry of all the food boluses, then the peristalsis resumes in order.

Lower esophageal sphincter relaxation :

It is the distal most part of the esophagus with a zone of high pressure even at resting state. Various factors are attributed to the resting high basal tone of the LES.

Myogenic tone is increased as the LES sphincter has increased proportion of alpha – actin in comparison to the esophagus. The muscles cells even at resting state have spontaneously opened chloride channel. This maintains a depolarised state with constant influx of calcium ions. Relaxation of LES begins with 2 seconds of relaxation of the UES. As the food bolus reaches the LES, it elongates and effaces forming an ampulla. Following the transit of the bolus it immediately contracts and the LES pressure remains higher than the intra-gastric pressure, till the next wave of peristalsis.

Interstitial cells of cajal :

Interstitial cells of Cajal, otherwise known as pacemaker cells of the gut. As explained earlier, they are situated in the myentric plexus of Auerbach. Peristalsis in the smooth muscle is a sophisticated mechanism involving the central nervous system and the intrinsic nervous system. Descending inhibitory reflex in an important phenomenon which enables smooth propagation of peristalsis. These complex neural transmissions are thought to be modulated by the interstitial cells of Cajal. As of now, it is understood that the post ganglionic nerve fibres release neurotransmitter which directly act on the muscle fibres. However, now there are evidence pointing towards a system where the post-ganglionic fibres synapse with the interstitial cells of Cajal which in turn relays the impulse to the smooth muscles(19).

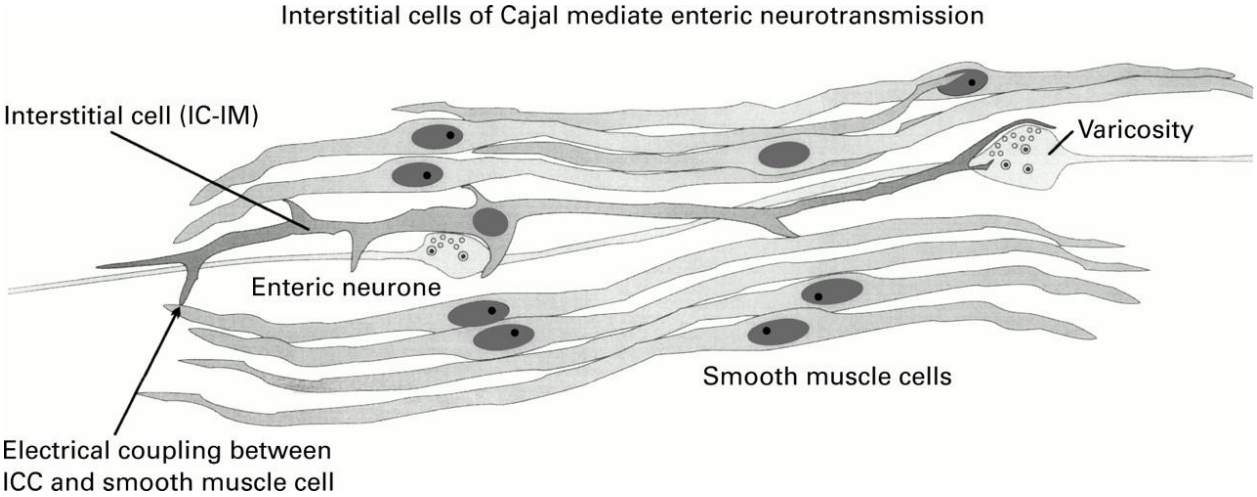


Figure 11: Relation of interstitial cells of Cajal, enteric nervous system and smooth muscles

Histology of achalasia :

As it is evident that the primary pathology is absence of progressive peristalsis and failure of relaxation of the lower esophageal sphincter, histopathological studies are conduction in a few centres worldwide. Goldblum et al has the largest series of histopathological studies done in 42 patients who underwent esophagectomy for achalasia. He noticed loss of ganglion cells were noted in 52% of the specimens. It was associated with various grades of inflammation and fibrosis which brought to the supposition that the inflammation occurred early in the natural history of the disease(20). Smooth muscle cell hypertrophy was also noted. It was attributed to the loss of nitriergic inhibitory neurons which was confirmed in experiment studies on NO synthase knocked out mice with similar recordings (21). Electron microscopic studies have suggested have suggested increased in eosinophil in achalasia and the

retained food debris resulting in mucosal injury was attributed for the increased antigen exposure. Interstitial cells of Cajal have been noted to be in close proximity of the myentric plexus neurons and immunohistochemical analysis have shown decrease in c-kit expression suggesting a probable primary pathology of the interstitial cells of Cajal.

Etiology of achalasia :

There is no one proven etiological factor for this disease. In fact all the treatment modalities aimed at this disease are palliative in nature as we do no treat the primary pathology. Pathological process in the central nervous system or extrinsic neural loss as the primary pathology is ruled out as there is no consistent evidence in case reports and also in experimental studies. Intrinsic loss of neurons secondary to inflammation was considered. The following are some of the theories proposed:

1. Inflammatory secondary to viral infection: Only measles virus association was proven to be statistically significant in studies, however the causal relationship could not be ascertained.
2. Chronic obstruction: This was thought to be the reason for long as many patients with obstruction at the gastroesophgeal junction loss peristalsis and in some of them when the obstruction is relieved via a myotomy, peristalsis regained. This theory was tested in animal models with moderate success.

3. Chronic neuronal degeneration: This was proposed as there were case reports of Parkinsonism associated with dysphagia. Interestingly, both achalasia and Parkinsonism patients with dysphagia had increased Lewy body deposition. But the manometric findings of these patients were not as that of achalasia.
4. Familial : It was thought to be an autoimmune disease due to the following features

    (i) Anti-myentric IgG antibodies were noted to be significantly increased in achalasia (22).

    (ii) Increased inflammatory cells infiltration was noted in around the myentric plexus region as evidenced by electron microscopic and immunohistochemical analysis(23)

    (iii) Increased prevalence of HLA class II antigens(24).

Evaluation

In patients suspected to have achalasia, further evaluation is required to confirm the diagnosis. Manometry is diagnostic for achalasia. Barium esophagogram is indicated if the manometry is inconclusive. Upper gastrointestinal scopy should be done in patient suspected to have secondary achalasia.

Manometry:

It is the gold standard for diagnosis of achalasia cardia. There are two types of manometry. There are two types of manometry.

A) Conventional manometry:

Characteristic feature of achalasia in conventional manometry is absence of relaxation of lower esophageal sphincter and aperistalsis.(25)

- Basal lower esophageal sphincter pressure falls in response to swallow. Normally it falls to a level of 8mmhg above the gastric pressure. If the basal lower esophageal pressure remains >8mmhg above the gastric pressure, it is diagnostic of achalasia.
- Aperistalsis is noted in the distal 2/3rd of the esophagus. Even though there may be minimal pressurisation in response to swallow, they are non-sequential with amplitude less than 40mmHg.

B) High Resolution Manometry (HRM)

In contrast to conventional manometry where sensors are spaced at 3 to 5 cm intervals, HRM sensors are typically spaced 1 cm apart along the length of the

manometric assembly. Catheters with up to 36 sensors distributed longitudinally and radially in the esophagus allow for simultaneous pressure readings spanning both sphincters and the interposed esophagus. Esophageal pressure topography (EPT) is a three-dimensional plotting format devised for depiction of HRM studies. EPT interpolates pressure values between sensors to create a pressure continuum. Pressure magnitude is converted into a color scale using 'cold' colors to denote low pressures and 'hot' colors to denote higher pressures.

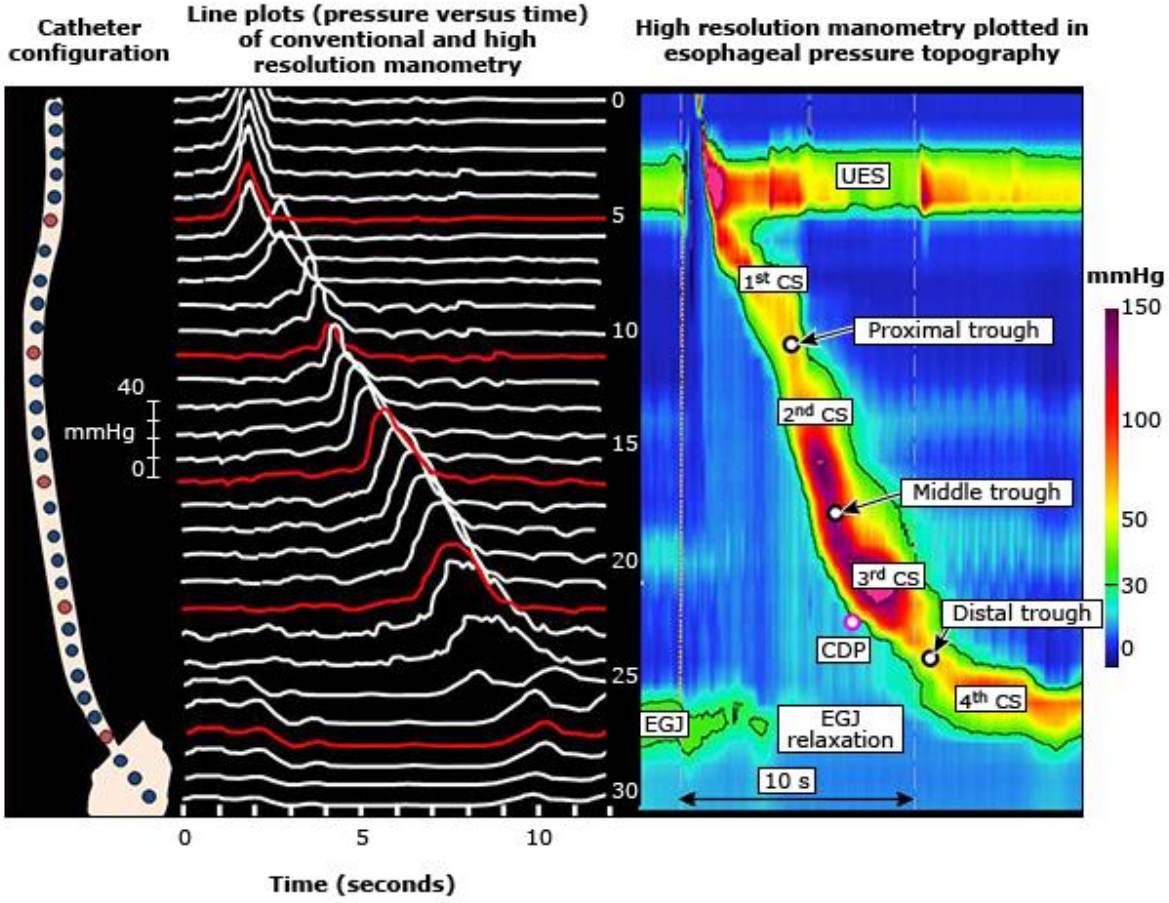


Figure 1 : High resolution manometry (Courtesy – uptodate - HRM)

The result is a seamless isobaric contour (IBC) map spanning from the upper esophageal sphincter to the esophagogastric junction (EGJ). This also allows for the

depiction of real-time luminal pressure gradients and spatial transition points of contraction amplitude or propagation velocity along the esophagus that correlate with anatomical and physiological landmarks.(26)

Analysis of the HRM includes the following:

Contractile segments:

Topography of HRM shows four contractile segments.(27)

First contractile segment : Upper esophageal sphincter contraction .

Second and third contractile segment: Contraction of the body of the esophagus

Fourth contractile segment : Lower esophageal sphincter

Transition zone:

A pressure trough noted between the 1st and 2nd contractile segment which is labelled the "transition zone"(28). This is also identified as the region of transition of neurological control. Proximal to this zone, the peristalsis is controlled by the central nervous system and distal to this zone the control of peristalsis is taken over by intrinsic nervous system(29).

Contractile deceleration point (CDP) :

The velocity of contraction is rapid in the proximal esophagus corresponding to the rapid transit of food bolus. At a certain near the esophagogastric junction, the velocity and the propagation of the food bolus slows down. This marks the onset of formation

of the phrenic ampulla, a distinct feature of the lower esophageal sphincter which transiently becomes effaced and elongated(30). (Figure 5)

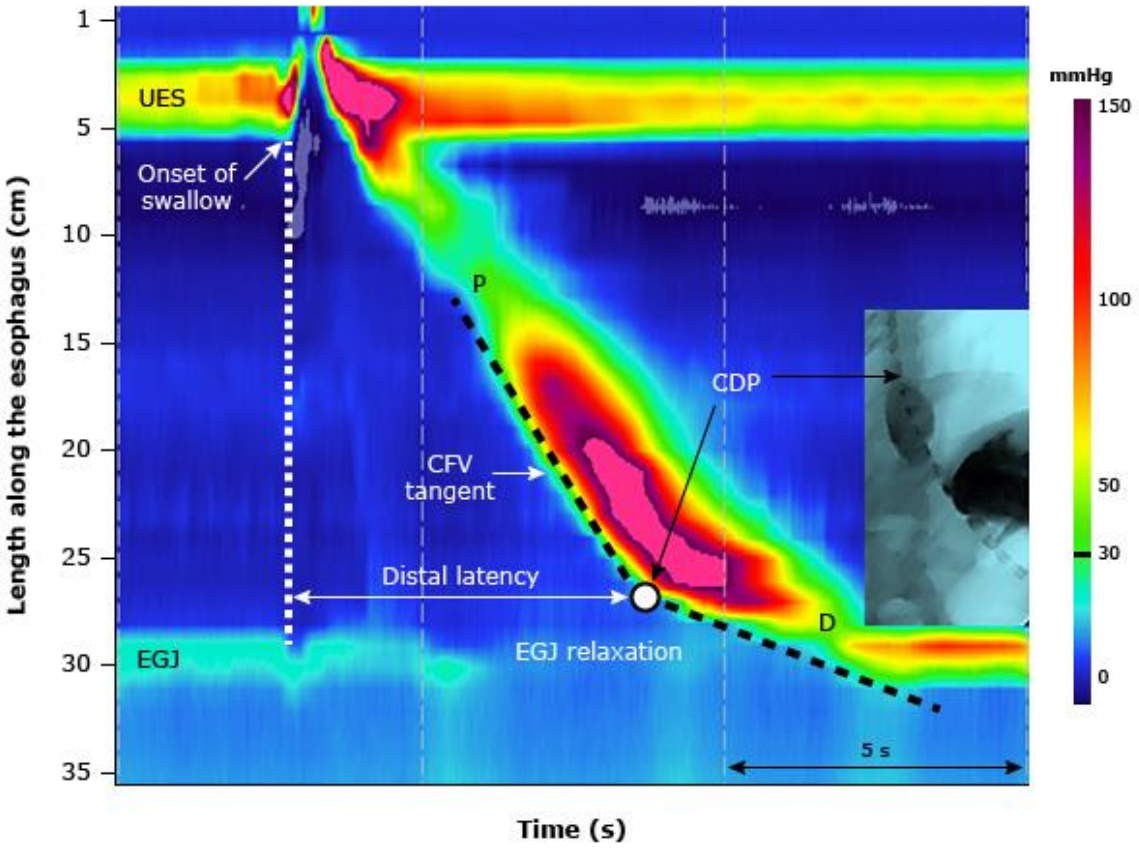


Figure 2 : Contractile deceleration point (CDP) (Courtesy –Uptodate –HRM)

Integrated Relaxation Pressure :

Normally, the lower esophageal sphincter relaxes in response to a swallow to facilitate passage of food bolus. Absence of relaxation of the LES is expected in achalasia which is translated as raised intraluminal pressure in the manometry. Raised intraluminal recording could be due to a confounding factor such as an external compression from the crural diaphragm. As it is not possible to distinguish between

external compression and impaired relaxation of the lower esophageal sphincter based on the pressure readings, a complex metric, known as the integrated relaxation pressure is formulated.

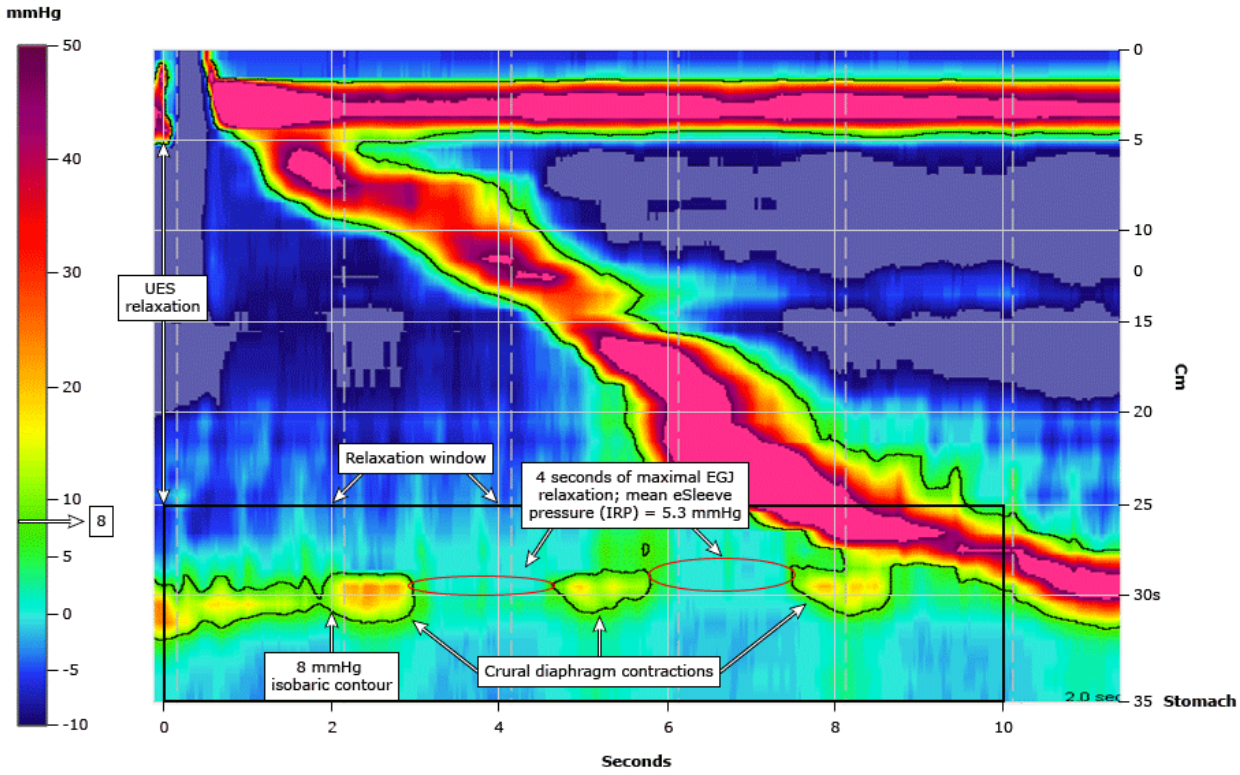


Figure 3 : Integrated Relaxation Pressure (Courtesy : Uptodate – high resolution manometry)

Time in seconds is plotted at the x- axis and the pressure on the Y-axis (figure 6). Following upper esophageal sphincter relaxation, a time window of 10 seconds is considered. In this time window, a four second the time frame of esophagogastric junction relaxation was noted (contiguous or non-contiguous). The LES pressure during this period of relaxation was calculated and its mean is recorded as IRP. Basically, it is defined as the average minimum pressure at the esophagogastric junction for four seconds of relaxation within 10 seconds of swallowing (upper sphincter relaxation). The upper limit of normal IRP is 15mmhg (31).

Contraction : Any lumen obliterating pressure recorded in the manometry is called contraction. Basically, the circular smooth muscle layer constricting down the pressure transducer.

Pressurisation: This denotes the pressure recorded within an open; for example between closed upper and lower esophageal sphincter. It is represented as a vertical band in the topography of the HRM (32).

Based on the HRM, achalasia is classified into three types(33).

- Type I – Median IRP >upper limit of normal, 100 percent failed peristalsis, minimal pressurization within the esophagus.
- Type II – Median IRP >upper limit of normal, no normal peristalsis, pan-esophageal pressurization with ≥20 percent of swallows.
- Type III – Median IRP >upper limit of normal, no normal peristalsis, preserved fragments of non-propagating distal peristalsis.

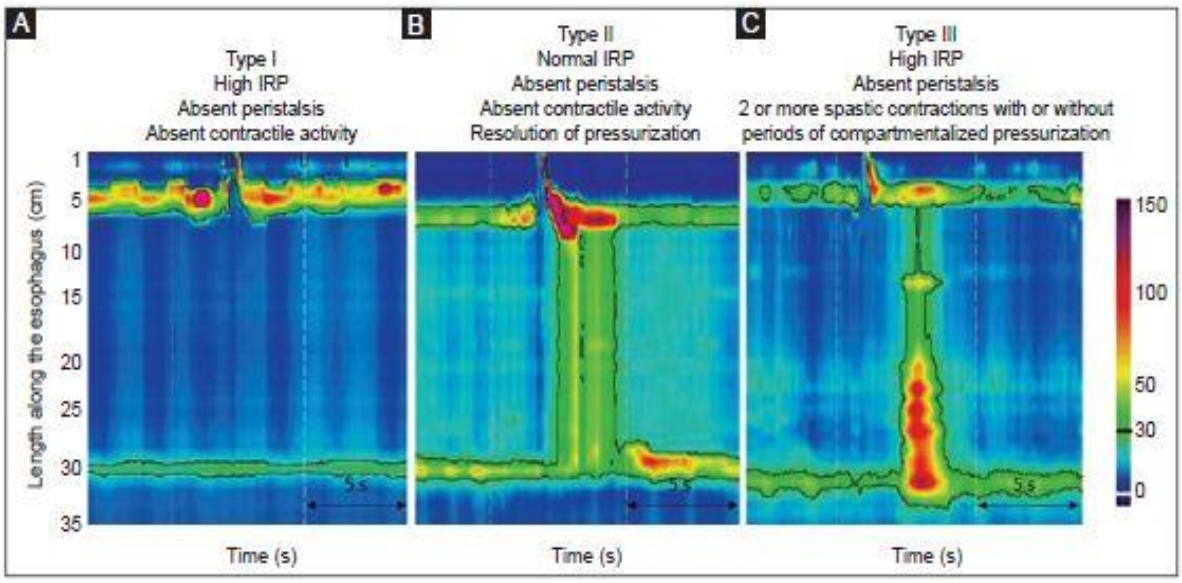


Figure 4: Chicago classification of achalasia(courtesy: Annals of Gastroenterology (2015)

Imaging: Barium esophagography

As manometry is diagnostic of achalasia, Barium study is not indicated in all patients. Barium esophagogram may be falsely negative in 30% of the cases(34). In earlier stages of the disease, narrow esophagogastric junction seen as bird-beak appearance and aperistalsis can be seen. In advanced cases, significantly dilated and tortuous esophagus described as mega-esophagus or sigmoid esophagus is noted. Occasional sudden burst of peristaltic activity can be seen and it is described as Hurst phenomenon.

Imaging: Chest X ray

Dilated esophagus can be seen as widening of the mediastinum with absence of fundic air bubble.

Upper gastrointestinal scopy:

Esophageal mucosa remains normal in achalasia. Due to stasis of food, esophageal candidiasis can be noted occasionally. Lower esophageal sphincter is usually occluded and it does not open spontaneously as in normal individuals. However, the scope can be easily negotiated through the lumen with a gentle push and a characteristic ‘give’ can be experienced by experienced endoscopists. Upper gastrointestinal scopy is more relevant if there is a suspicion of malignancy causing a secondary achalasia.

Management of achalasia:

Achalasia has been known to mankind for more than 300 years. In 1674, Sir Thomas it was treated by dilatation of the esophagus using whale bone. Treatment approaches have evolved over the years. Currently the options available are medical, minimally invasive and surgical.

I) Pharmacological therapy:

Relaxation of the lower esophageal sphincter using pharmacological agents such as nitrates(isosorbide dinitrate 5mg) and calcium channel antagonists(nifidipine 10mg to 30mg) have been tried with unsatisfactory results(35). It is also associated with significant side effects like headache, hypotension. Eventually tachyphylaxis occurs rendering it useless. Other drugs like 5-phosphodiesterase inhibitors (sildenafil), anticholinergics (dicyclomine) and beta adrenergic agonists (terbutaline) have been tried but there is no evidence to prove its efficacy. It can be however used as mode of treatment when the patient is not fit for operation or pneumatic dilation or while being evaluated or waiting for definitive management of achalasia(36).

II) Minimally invasive management:

Two most widely utilised modes of minimally invasive techniques are pneumatic dilatation and botulinum toxin injection.

A) Pneumatic dilatation :

Principle:

Dilatation of the lower esophageal sphincter results in stretching of the muscle fibres thereby decreasing the pressure. Initially it was practiced using bougies and the

dilators have evolved over the years from mechanical dilators, to hydrostatic and of late pneumatic balloon dilators.

Technique:

Dilatation is done under anaesthesia or conscious sedation. There is still controversy and varied opinion among experts regarding the pressure to be used, rate of dilatation, duration of initial dilatation and number dilatations. However the most commonly practiced method is identification of the LES using manometry and then 120mL of air at a pressure of 7 psi for a duration of 60 seconds followed by rapid release of pressure.

Outcomes:

Short term relief of dysphagia is as high as 85% following pneumatic dilatation(37). However, the long term results were not as promising as the short term benefits. This is proven in a prospective study for 18 years in a single centre. They noticed relapse rates were 18% by 2 years; 41% by 5 years and 60% by 10 years. Moreover, 43% patients underwent additional treatment such as repeat pneumatic dilatations and myotomy(38).

B) Botulinum toxin injection:

Intra-sphincteric injection of botulinum toxin injection has been a practiced for treating achalasia. It is a type A botulinum toxin derived from clostridium botulinum. It inhibits acetylcholine from the nerve endings thereby resulting in reduction in LES pressure(39). The short term effects are comparable with pneumatic dilatation or myotomy(40), however, the effect wane of within months requiring repeated injections within 6 months of injection(41).

C) Per-Oral Endoscopic Myotomy (POEM):

This is a new technique where natural orifice is utilised for the operation (Natural orifice trans-luminal endoscopic surgery). Short term results reveal its efficacy up to 90% in relieving symptoms. There are not enough evidence regarding long term outcomes to recommend this treatment modality(42,43). This safe and effective procedure. Studies done revealed good short term outcomes of dysphagia relief and it is comparable with laparoscopic Heller's myotomy(44). Acid reflux is however noted to be high after endoscopic myotomy(45).

III) Surgical management:

Operative management of achalasia was first described by Ernst Heller in 1913. He described a double cardiomytomy (anterior and posterior myotomy). In 1923, it was modified to just an anterior cardiomytomy. Success rate was 90% to 95%. Principles of operative management would include the following.

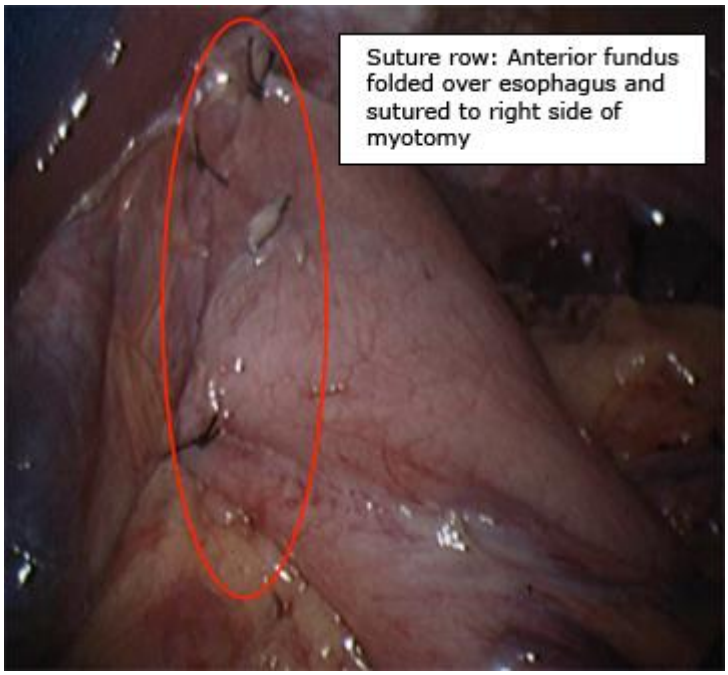
- Reduction in the LES pressure with adequate cardiomyotomy.
- Prevention of gastroesophageal reflux in the post-operative period.
- Prevention of scarred closure of myotomy site.

Initially this was through thoracic approach. In 1991, thoracoscopic approach was introduced which resulted in decrease in the post-operative pain and the number of days of hospital stay. Anti-reflux procedures were not recommended during that time as there were no evidence to support it (25,26).

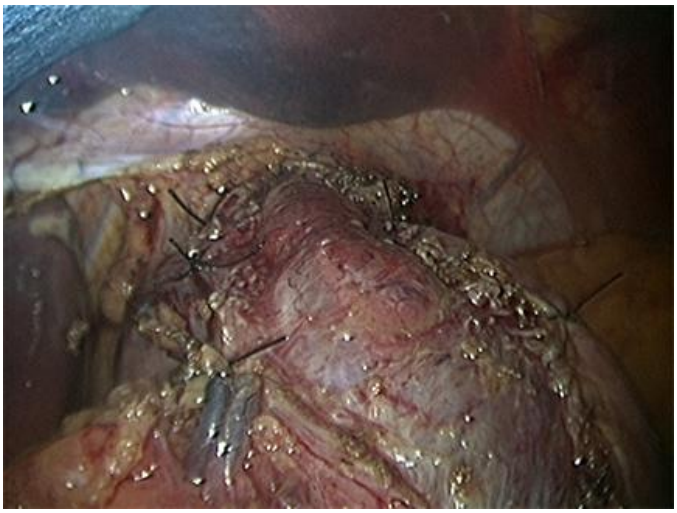
Subsequently in the mid-1900s laparoscopic approach became popular for two reasons. Firstly, gastric extension of myotomy was considered crucial to prevent post-operative dysphagia. Secondly, anti-reflux procedures can be following the myotomy. Thirdly, post-operative hospital stay was lesser in patients undergoing laparoscopic myotomy. Thus, laparoscopic modified Heller's myotomy with fundoplication is the current treatment of choice for achalasia(40,46–50). Robotic approach have been tried and the results showed statistically significant reduction in the mucosal perforation rate, however there was a strong suspicion of bias in these studies as the mucosal perforation rates following robotic surgeries were compared with the perforation rates of the laparoscopy myotomy done earlier in their learning curve(51).

- Extent of myotomy: Initially, a limited gastric myotomy was performed. A retrospective analysis done in a centre in Washington revealed 80% of patients who underwent limited myotomy (0.5cm to 1cm) had pathological levels of acid reflux and 17% of them had symptoms of dysphagia. Extension of gastric myotomy 1.5 to 2.0 cm was done in these patients who presented with dysphagia following the initial surgery. Fifty percentage of them had improved results. Subsequently, the next four years, 1.5cm to 2.0 cm myotomy was done and which resulted in a 90% success rate, however, few had recurrence of symptoms. Therefore a full 3cm was gastric myotomy was done(52). The current recommendations by SAGES is at least 4cm of myotomy on the esophagus and 2cm on the stomach(53).

- Anti-reflux procedure: This has been of concern and a matter of debate for long as there was conflicting opinion regarding performing fundoplication simultaneously during the myotomy. Some believed that adding a wrap procedure would defy the primary intent of preventing dysphagia and other believed that adding a wrap procedure would improve the quality of life by reducing reflux symptoms following myotomy.



Picture 21 : Dor fundoplication (courtesy- university of Washington)



Picture 21 : Toupet fundoplication (courtesy – University of Washington)

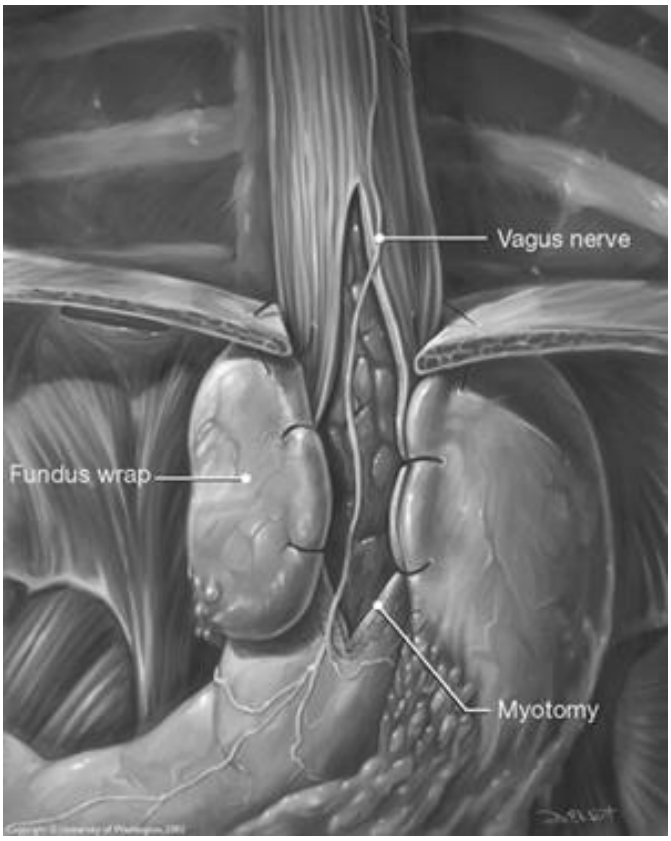


Figure 5: Toupet fundoplication (courtesy – University of Washington)

Meta-analysis has shown statistically significant increase in reflux symptoms in patient who did not have a fundoplication. It also showed a statistically significant

reduction in the 24 hour pH levels in patient with fundoplication. Though the need for anti-reflux procedure is well estabilished, it is still unclear as to which one is the best. Anterior 180 degree Dor fundoplication (figure 8) and posterior 270 degree Toupet (Figure 9 and 10) have statistically significant reduction in post-operative dysphagia when compared with a floppy Nissen's 360 degree fundoplication. There is no significant difference in the reflux symptoms. A meta-analysis comparing Dor and Toupet fundoplication revealed no statistically significant difference in terms of acid reflux or dysphagia(54). Dor fundoplication is preferred by many surgeons as it requires lesser dissection at the gastro-esophageal junction. Also anterior wrap serves as a buttress if any repair of inadvertent mucosal injury is performed.

Predictors of outcomes after myotomy :

Several studies have looked into the predictors of poor outcomes but the results were not consistent. Some of the noted factors are the following(55,56).

Positive predicting factors:

1. Achalasia type II.
2. Younger age (<40 years).
3. LES pressure more than 30mmHg.

Negative predicting factors:

1. Severe pre-operative dysphagia.
2. Low pre-operative LES pressure (<30mmHg).
3. Sigmoid esophagus.
4. Balloon dilation before myotomy.
5. Botulinum injection before myotomy.

6. BMI > 30

Treatment options following failed operation:

Failure rates after a myotomy is less, nevertheless when symptoms occur, it can be managed with botulinum toxin injection with a success rate of 71% in one year follow up. Other options are to do to redo laparoscopic operation which has satisfactory results. Pneumatic dilatation following a failed myotomy is generally avoided as there is an increased risk of mucosal perforation. If symptoms of refractory after trying these modalities, then esophageal resection with gastric pull up is the only viable option(53)

The following would summarize the treatment approach to achalasia cardia (57)

The following is the algorithm for management of achalasia cardia .

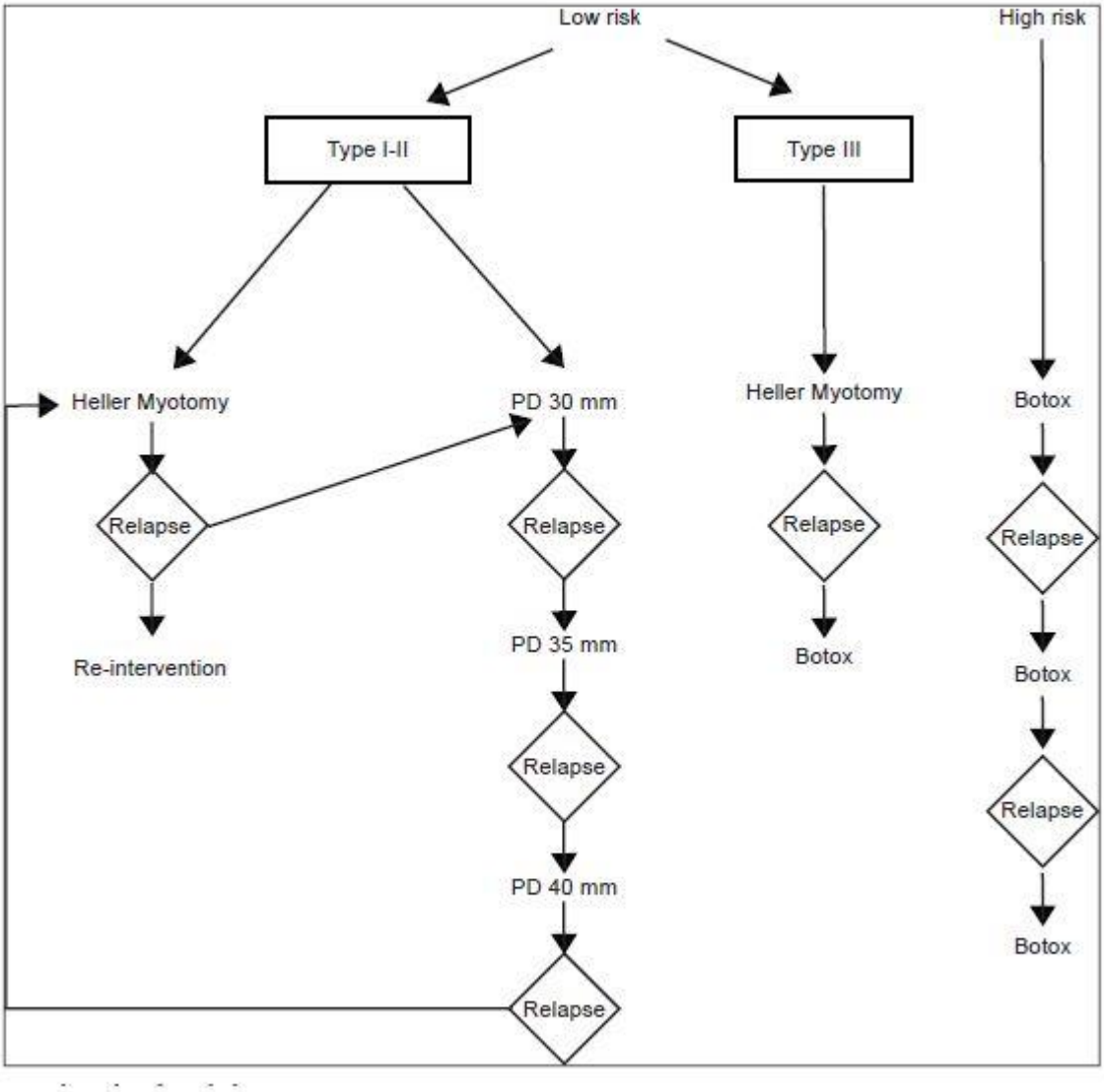


Figure 6 : Annals of Gastroenterology (2015)

Methodology

Setting:

This study was conducted in the department of Surgery, unit III, Christian Medical College Hospital, and Vellore. It was done in collaboration with the Institute of Pathology.

Study design:

This was a prospective observational study performed on patients undergoing laparoscopic Heller's myotomy between October 2012 to September 2014

Institutional review board and ethics committee approval:

The study design and the methodology was assessed by the institutional review board and the ethics committee and duly approved. The copy of the approval form is enclosed (Appendix 1)

Consent:

Patients diagnosed with achalasia were invited to take part in the study and the informed consent was presented in the native language. The consent forms used in the study was enclosed. (Appendix 2)

Inclusion criteria:

All patients who underwent laparoscopic Heller's myotomy during the study period who have consented to take part in the study were included.

Data collection:

The following was obtained from each patient.

1. Demographic profile of the patient
2. Preoperative dysphagia score
3. Preoperative investigations including barium study, endoscopy, HRM
4. Histopathological and immunohistopathological features of the oesophageal muscle biopsy
5. Electron microscopic features
6. Achalasia is classified based on high resolution manometry
7. Relief of dysphagia using dysphagia score

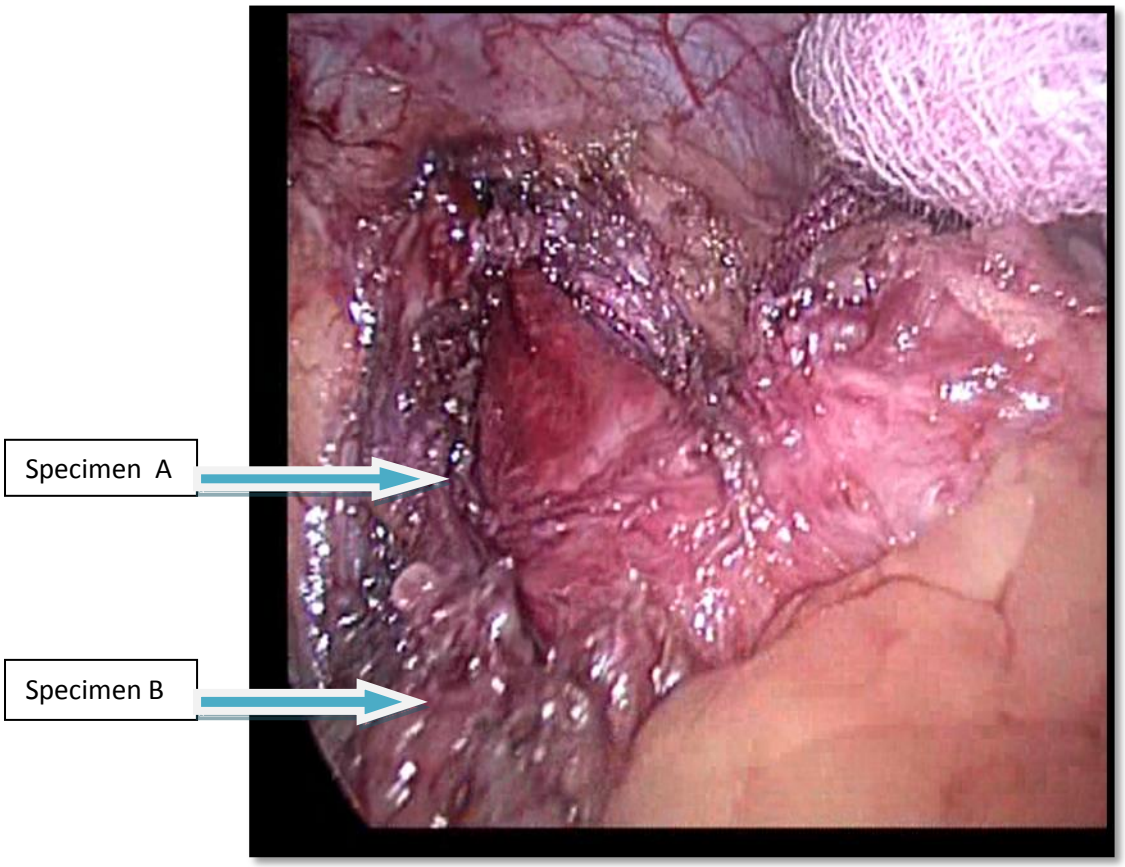
Sample size:

As this is an observational study, the sample size was based on the frequency that the procedure is being performed in our centre. A minimum sample size of 15 was planned.

Method of data collection:

Surgical procedure:

- All the patient were diagnosed with pre-operative manometry and barium study and taken up for the operation.
- Laparoscopic modified Heller's myotomy was performed. Entry was by four port technique.This involves dissection of the the connective tissue at the level of the esophageal hiatus followed by myotomy. It was extended up to 5cm in



the esophagus and 2cm onto the cardia. It is done meticulously to avoid perforation of the esophageal mucosa. The only additional procedure performed in these patients was

taking two small bits (0.5cm x 0.5cm each) of oesophageal muscle from the cut ends of the myotomy. If leak is encountered, it was primarily repaired with 5-0 polydiaxonine stiches. Anterior fundoplication was done irrespective of mucosal injury. Leak test or intra-operative endoscopy was not routinely performed. Drains were not usually placed.

- The specimen obtained is checked for cautery artefact on microscopic examination. As the sample obtained from the first patient revealed cautery artefact, the technique of obtaining the biopsy was modified to get a good quality tissue for the study. Standard myotomy was done using the cautery. The proposed site of biopsy was chosen and the muscle tissue was gently grasped and dissected using scissors. By doing this, we have one end of the muscle which does not have cautery effect. The specimen is put on a dissecting slab and the cut end of the muscle is carefully chosen and sent for further examination.
- The specimens obtained from the lower esophagus and the gastro-esophageal junction was labelled sample A and sample B respectively.
- The specimens thus collected were preserved in 3% gluteraldehyde and 10% formalin for Electron microscopic studies and Histopathology studies, respectively.

Processing of sample for electron microscopy:

1. Second fixation with 1% osmium tetroxide for additional stability during electron bombardment and decreases distortion.
2. It is degraded in series with ascending strength of alcohol.
3. Infiltrated by propylene oxide and eposy resin.
4. Embedded in siliconised rubber mould with epoxy resin.
5. Polymerisation is achieved by incubating the embedded mould at 60 degree for 48 hours
6. One micron thin sections cut through ultra-microtome (Leica ultra-cut UC7) with glass knife and stained with toluidine blue. It is further viewed in light microscopy which is called the one-micron study. The areas of interest are marked out for ultrathin microtome.

Picture 1: Leica EM UC7 microtome

7. Ultrathin sections were cut using a diamond knife. These sections are taken on copper grid and stained with uranyl acetate and Reylon's solution.
8. Philips Tecnai electron microscope used in this study.

Picture 2: Diamond diatome use for cutting ultrathin section.

Picture 3: Philips Tecnai – Transmission Electron Microscopy.

- The specimen used for histopathology is stained with haematoxylin and eosin to study the ganglion cells and inflammatory infiltrate. The slides were coded and kept for immunohistochemistry analysis using CKIT (CD 117) , the marker which is specific for Interstitial Cells of Cajal(ICC of the gut) and CD3, a marker of T lymphocytes.
- The histopathological features were graded by the pathologist. Ganglion cells were identified and quantified as 3 groups. “Rare, Few and Many”.

  “Rare” indicates the presence of occasional cells,

  “Few” indicates the presence of infrequent cells and

  “Many” indicates the presence of numerous cells.

  Fibrosis was graded as Mild, Moderate and Severe.

Follow up:

- Post-operatively, these patients were monitored till discharge and followed up at 1 month, 3 months and 6 months in the surgery OPD. Patient who were not able to come for outpatient visits were followed up with telephonic interviews. The short term surgical outcomes including complications and relief of dysphagia were recorded. Dysphagia was quantified using a dysphagia score:

  0-Able to eat normal diet / no dysphagia

  1-Able to swallow some solid foods

  2- Able to swallow only semi solid foods

  3-Able to swallow liquids only

  4- Unable to swallow anything

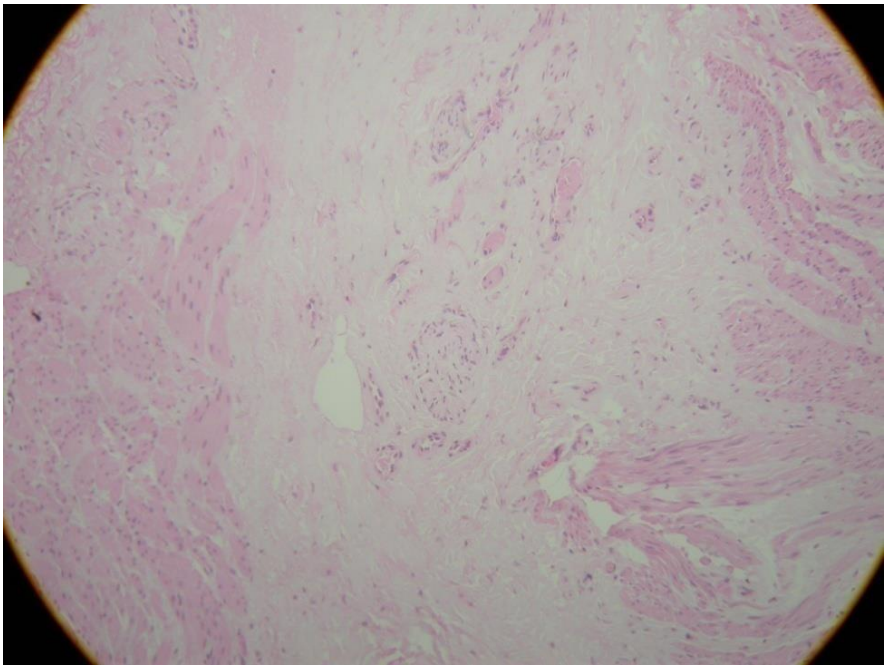
RESULTS

- Twenty one patients were recruited for the study. Intra-operative biopsy was obtained from 18 patients. The biopsy was adequate and representative in 17 patients. In one patient, the biopsy material was non representative. In three patients, intra-operative biopsy could not be done due to intra-operative difficulty. These patients were excluded from the analysis of histological parameters. So analysis was performed on 17 Pts.
- Haematoxylin and eosin staining and Electron microscopy study was done in samples obtained from the 17 patients.
- The following features were studied:
    1. Ganglion cells
    2. Nerve bundle hypertrophy
    3. Muscle fibres
    4. Perivascular fibrosis
    5. Inflammatory cells
- Immunohistochemistry analysis was done in samples obtained from 15 of the 17 patients.

H & E staining, immunohistochemistry and electron microscopy:

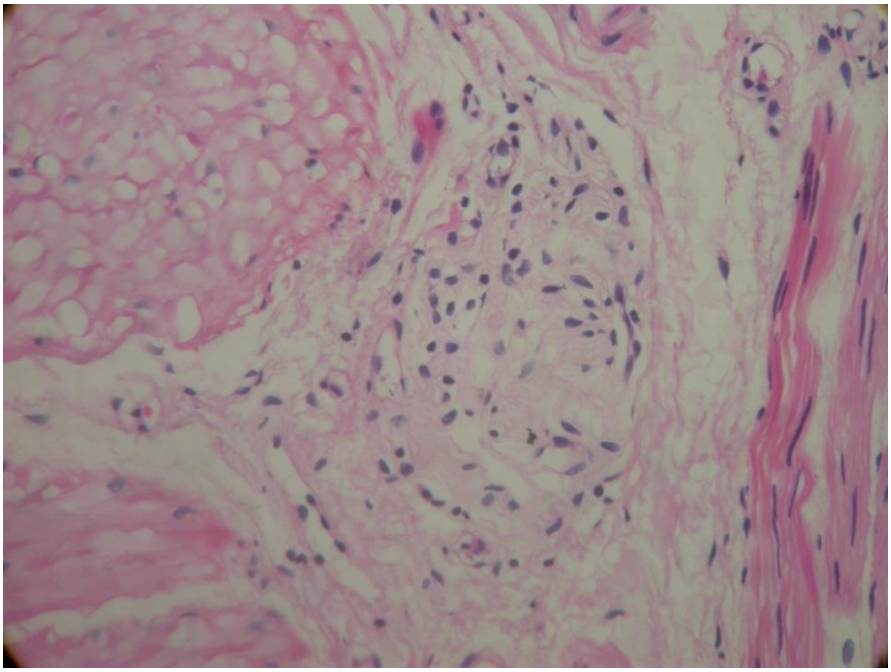
- H and E staining:

    1. Ganglion cells: 13/17 cases showed absence of ganglion cells. 4/17 cases had occasional ganglion cells. 1/17 case was excluded from the study as it showed only connective tissue.

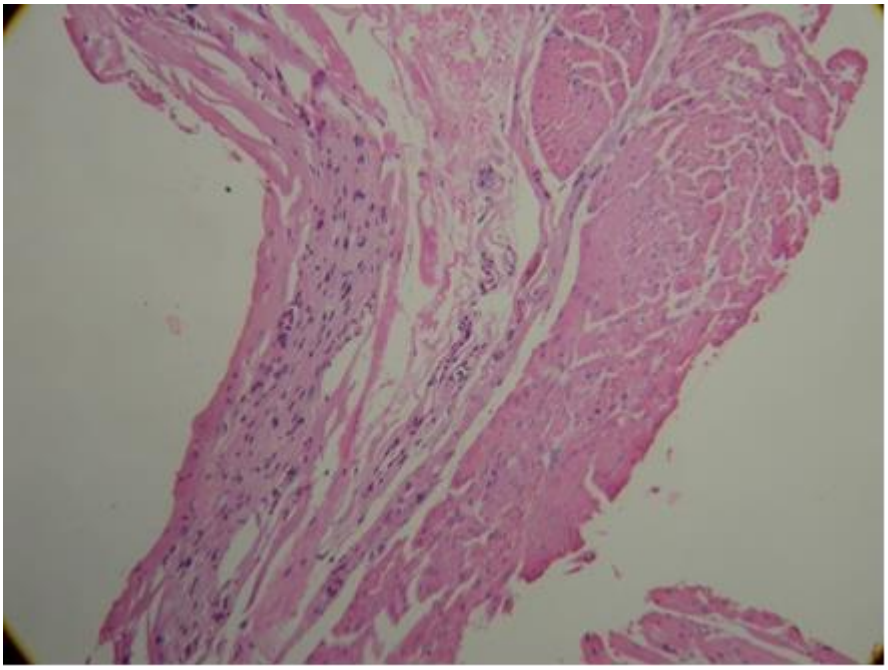


Picture 4 : Fibrosis of the myentric plexus

2. Nerve bundle hypertrophy: 3/17 cases showed mild hypertrophy. 7/17 cases showed moderate hypertrophy. 2/17 cases showed severe hypertrophy.3/17 cases revealed normal nerve fibres. In 3/17 cases nerve bundle could not be identified.

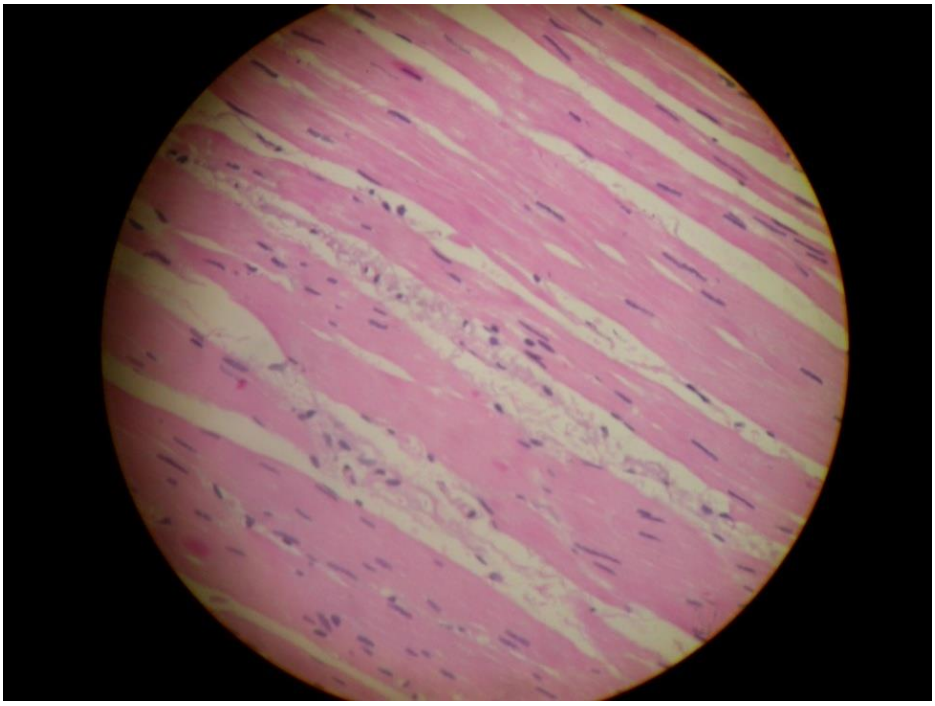


Picture 2A : Hyper trophy of nerve bundle : cross-sectional view

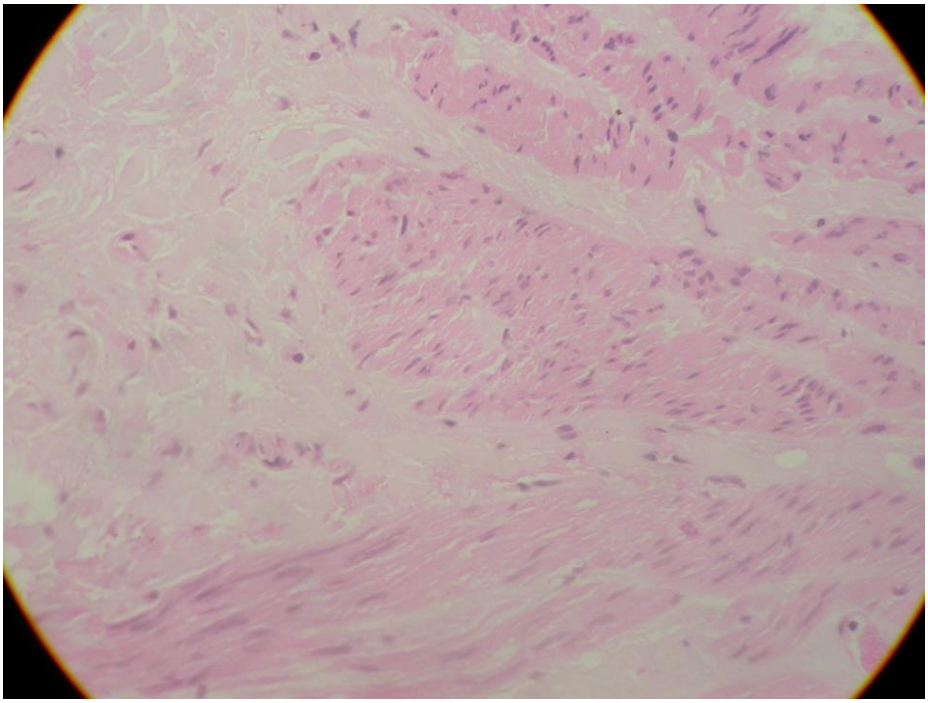


Picture 2B : Nerve bundle hypertrophy : longitudinal view

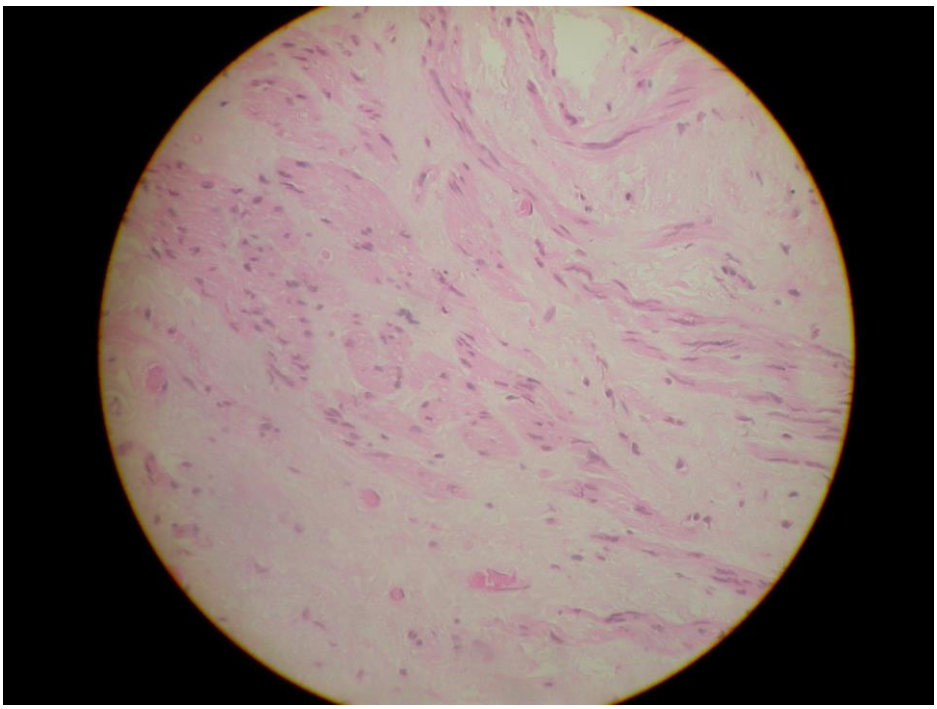
3. Muscle fibrosis: 8/18 cases showed mild fibrosis. 3/17 cases showed moderate fibrosis. 1/18 cases showed severe fibrosis. 3/17 cases showed no fibrosis. In 3/17 cases findings were inconclusive.



Picture 4A : Fibrosis of smooth muscles – mild



Picture 4B : Fibrosis of smooth muscles – moderate



Picture 4C: Fibrosis of smooth muscles – severe

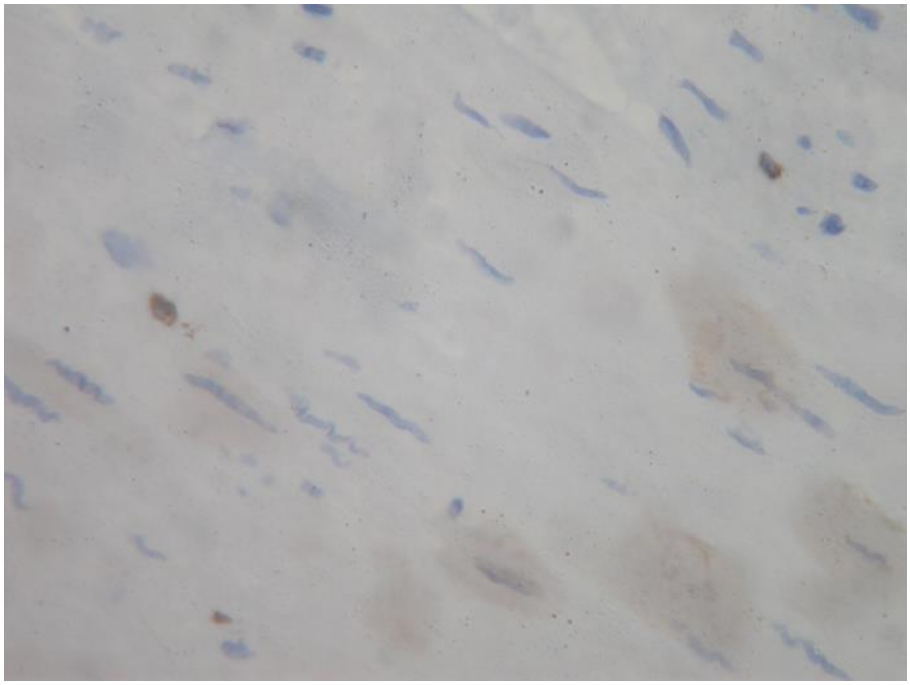
4. Perivascular fibrosis: 3/17 cases showed mild fibrosis. 2/17 cases showed moderate fibrosis. 1/17 cases showed severe fibrosis. 8/17 cases showed no evidence of fibrosis.
5. Inflammation: There was no evidence of significant inflammation in any of the cases.

IMMUNOHISTOCHEMICAL ANALYSIS:

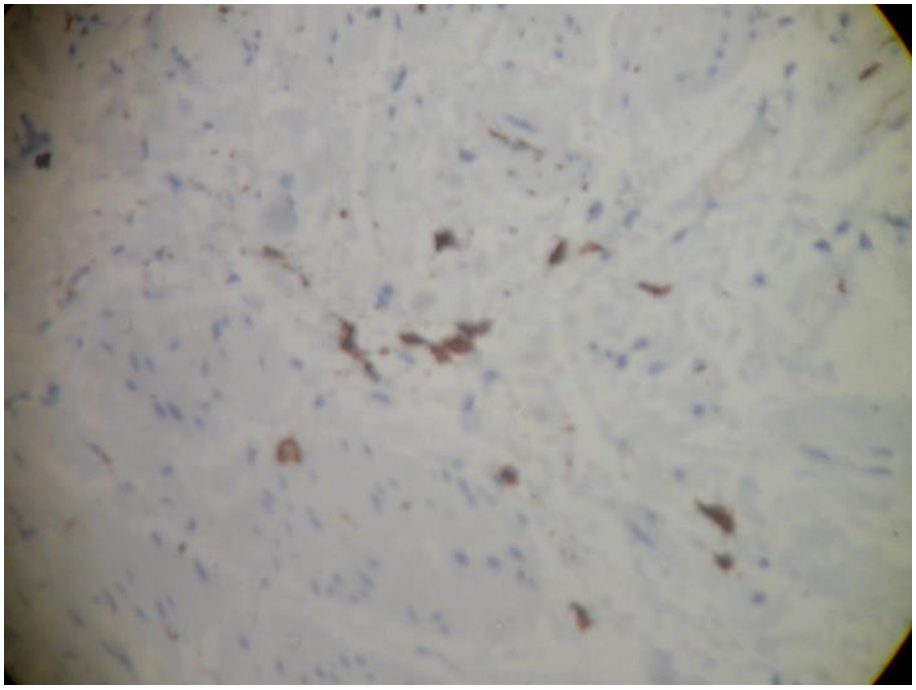
1. Inflammatory cells: They were found to be rare in 6/15 cases,

   Few cells were found in 2/15 cases and Many was found in 1/15 cases.

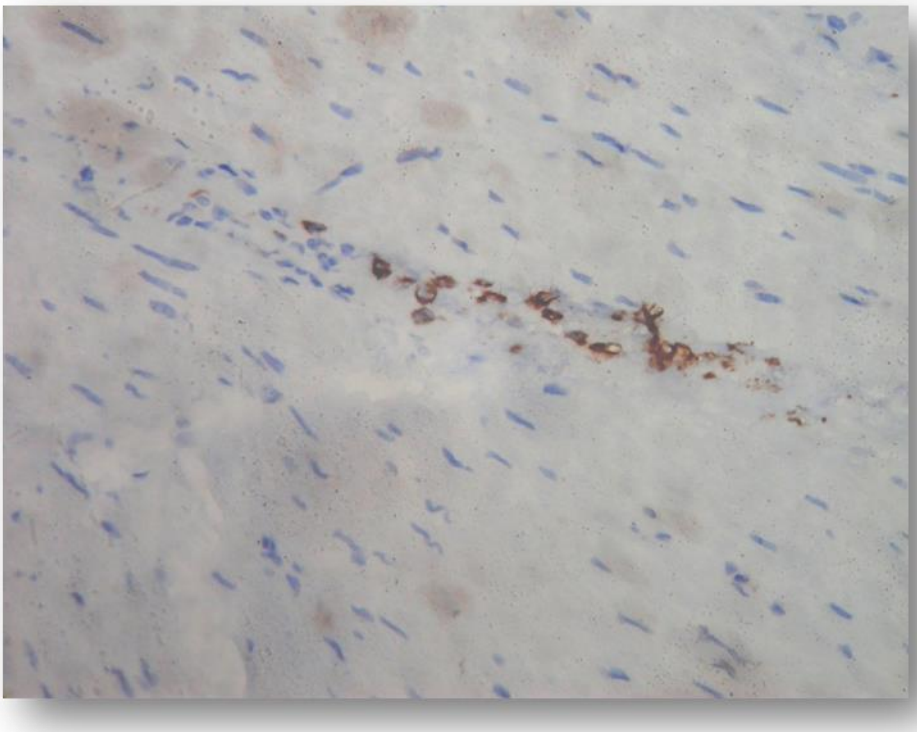
   They were absent in 2/15 cases. They were inconclusive in 4/15 cases.



Picture 5A : Inflammatory cells - Rare

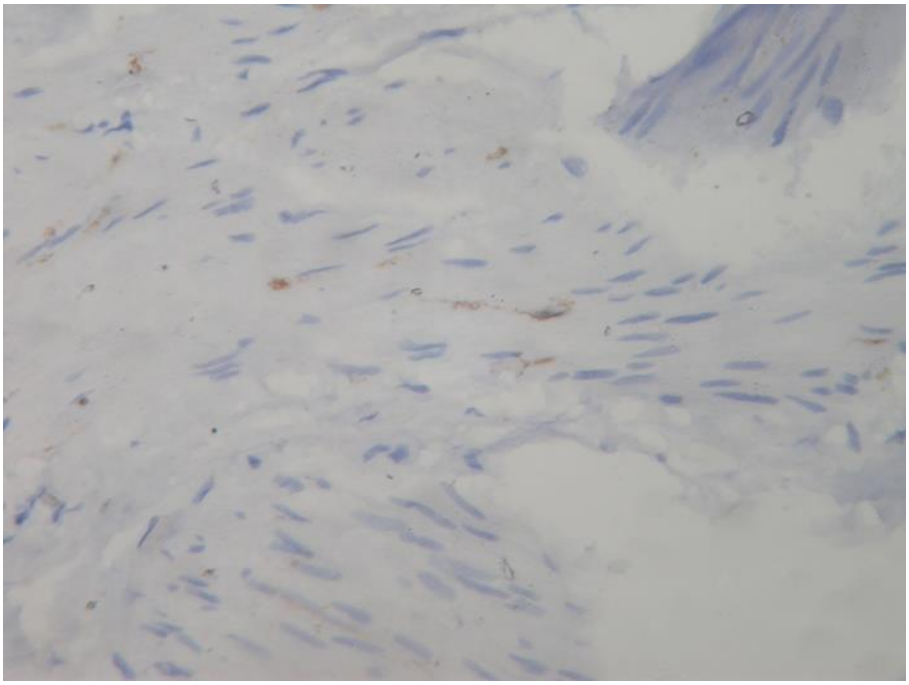


Picture 5B : Inflammatory cells – Few

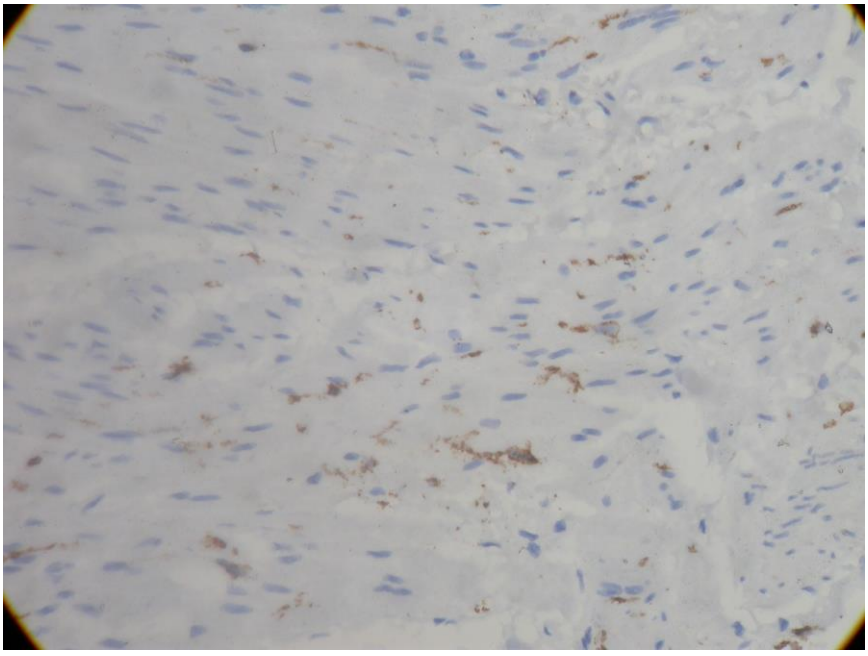


Picture 5B : Inflammatory cells – Many

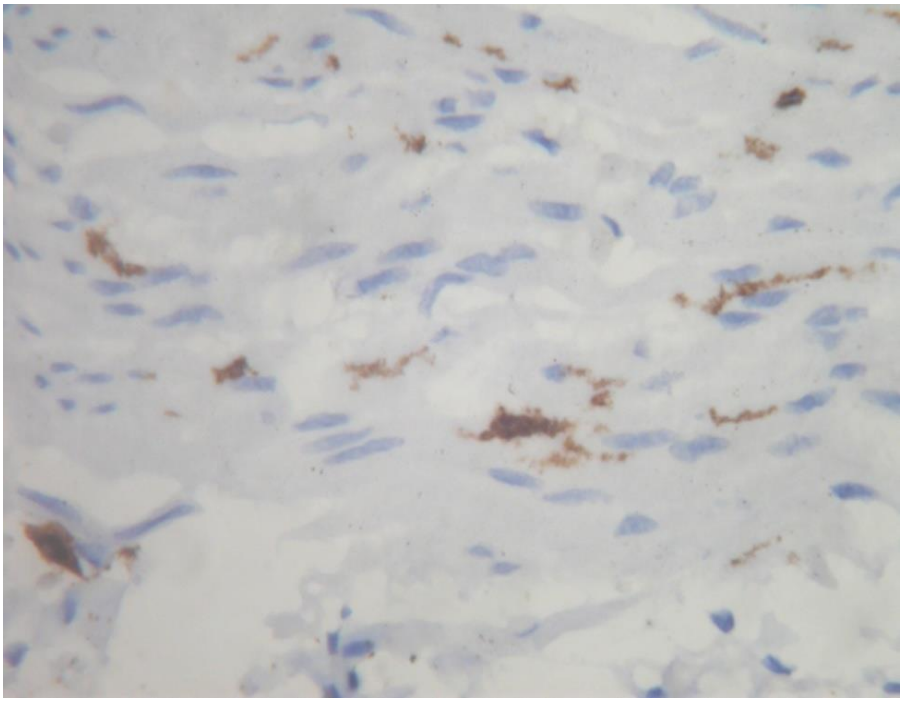
2. Interstitial cells of Cajal: They were rare in 3/15 cases, few in 1/15 cases and many in 5/15 cases, absent in 3/14 cases. 3/15 cases had inconclusive report.



Picture 6A: Interstitial cells of Cajal - Rare

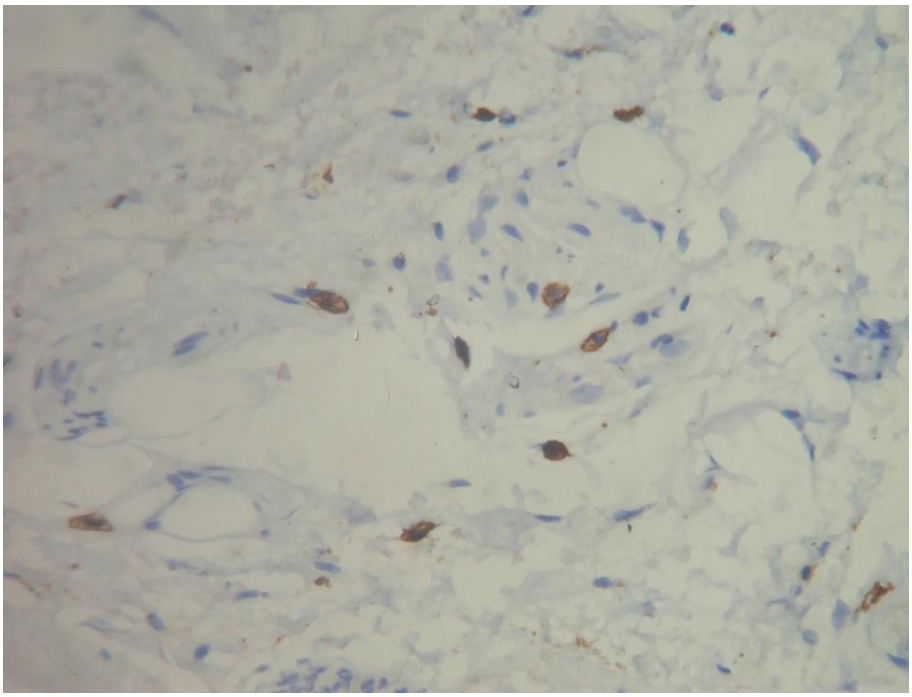


Picture 6B: Interstitial cells of Cajal - Few



Picture 6C: Interstitial cells of Cajal – Many

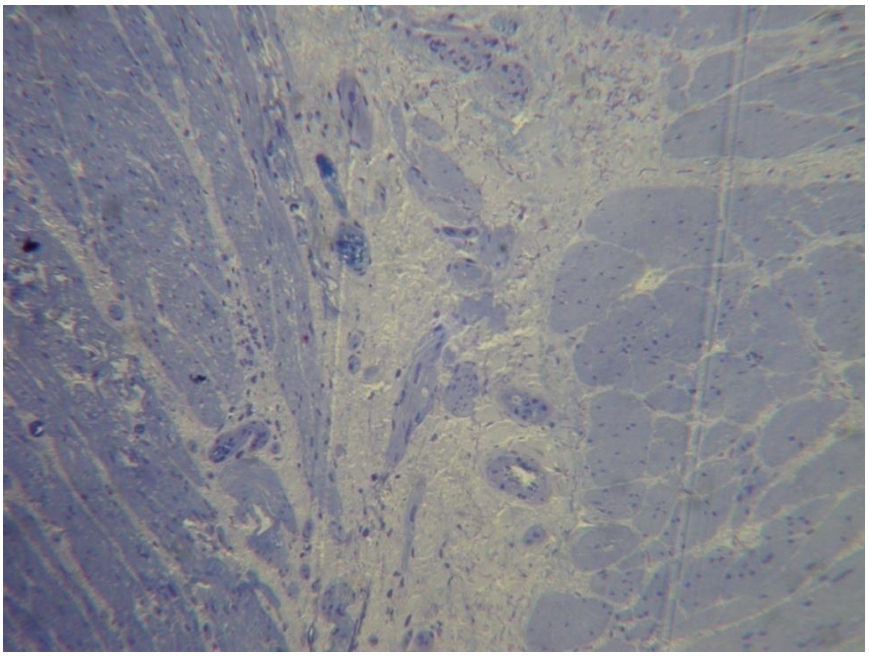
3. Mast cells: They were rare in 5/15 cases, few in 1/15 cases, many in 3/15 cases and absent in 3/15 cases.



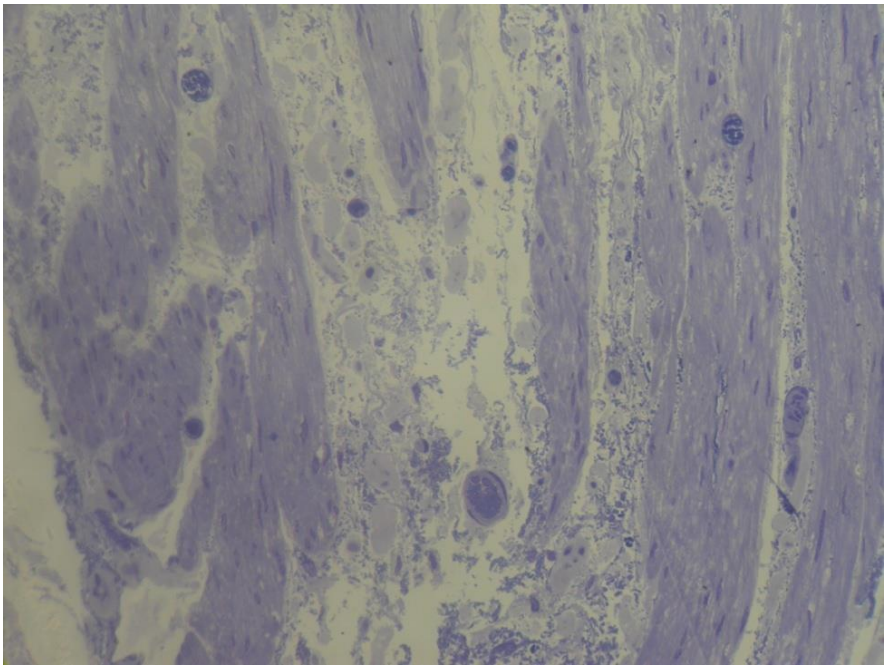
Picture 7: Mast cells.

ONE MICRON STUDY:

1. Ganglion cells: They were absent in all the cases.

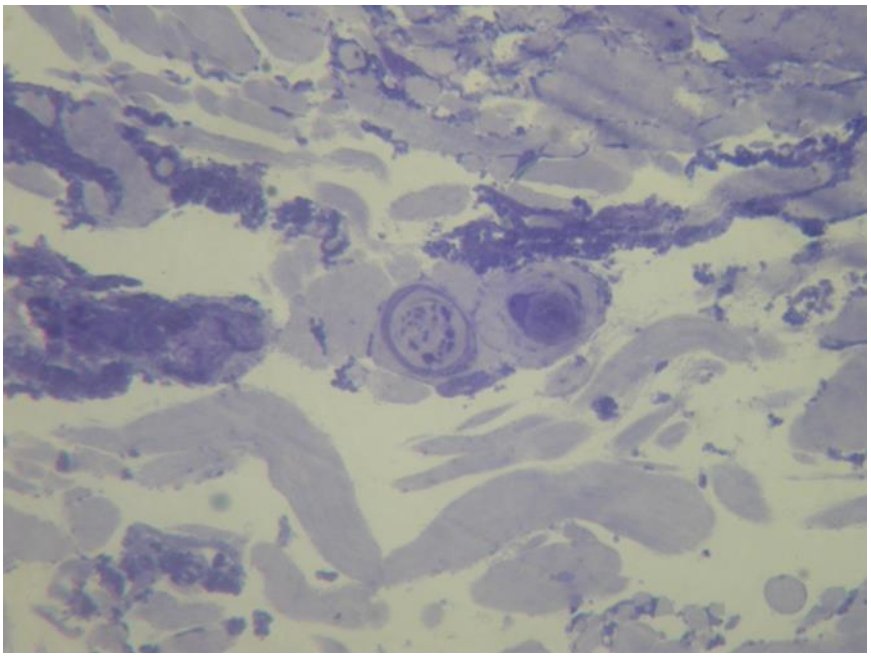


Picture 8 : One micron view of normal myentric plexus



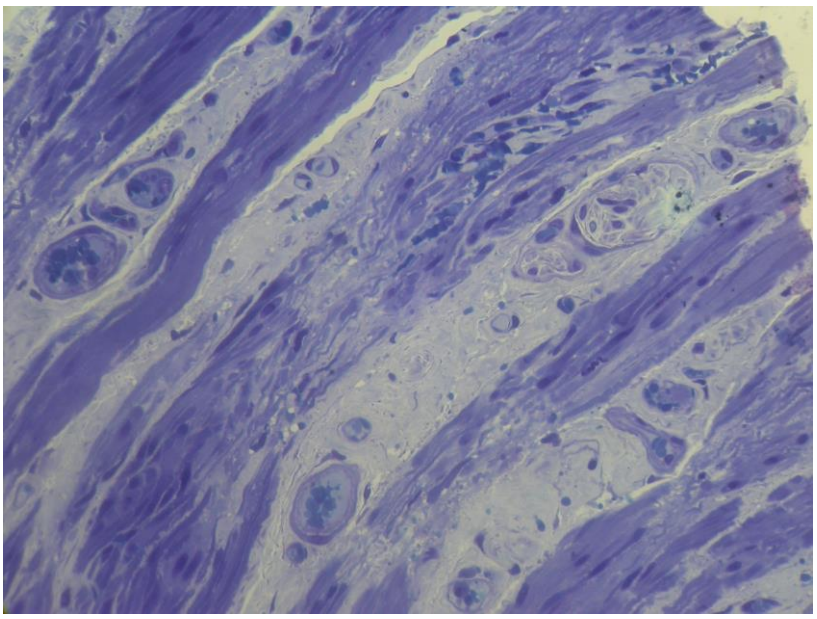
Picture 10 : One micron view of loss of ganglion cells in myentric plexus

2. Perineural fibrosis: It was absent in 2/17 cases. There was mild fibrosis in 11/17 cases, moderate fibrosis in 2 /17 cases and severe fibrosis in 1/17 cases. 1/17 was inconclusive.



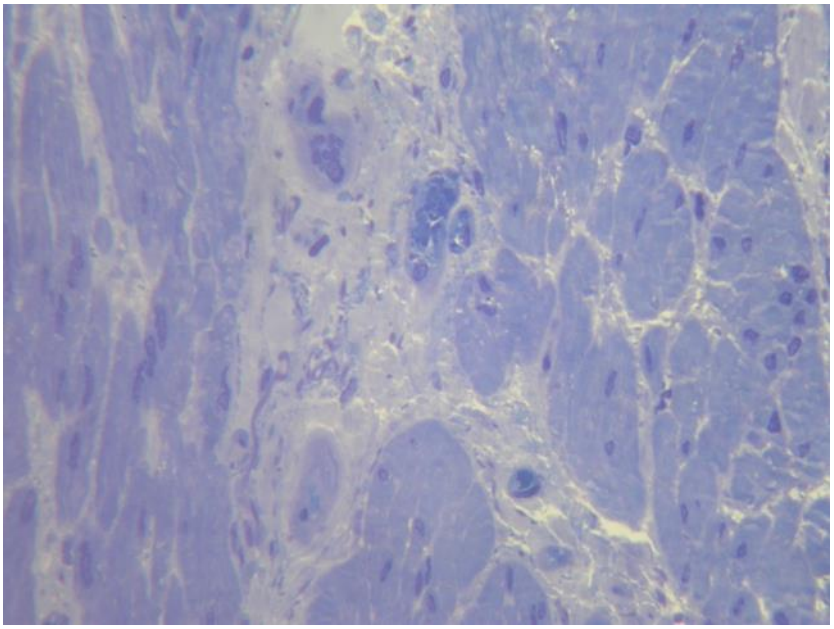
Picture 11: Perineural fibrosis

3. Muscle fibrosis: There was mild fibrosis in 2/17 cases, moderate fibrosis in 13 /17 cases and severe fibrosis in 1/17 cases. 1/17 was inconclusive.



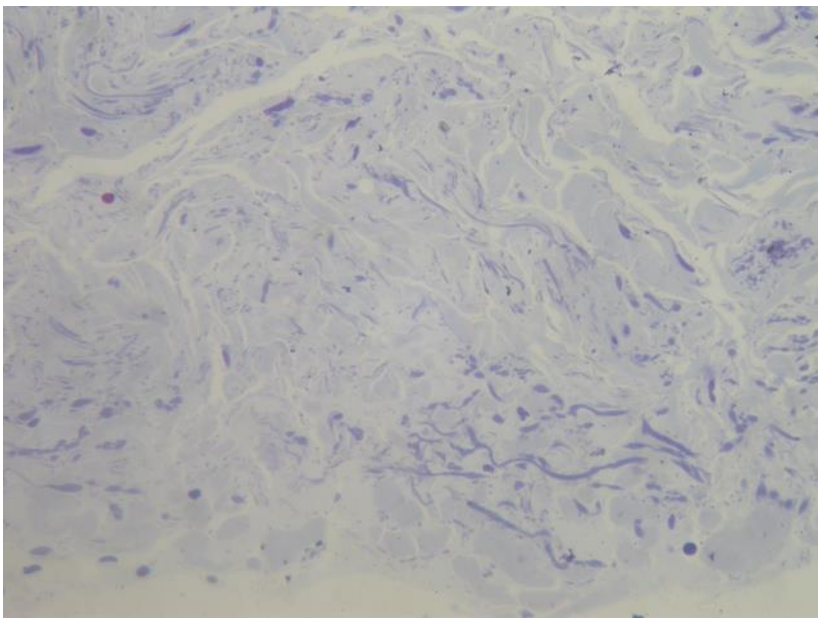
Picture 12 : Muscle fibrosis

4. Perivascular fibrosis: There was mild fibrosis in 6/17 cases, moderate fibrosis in 8 /17 cases and severe fibrosis in 3/17 cases.



Picture 13: Perivascular fibrosis

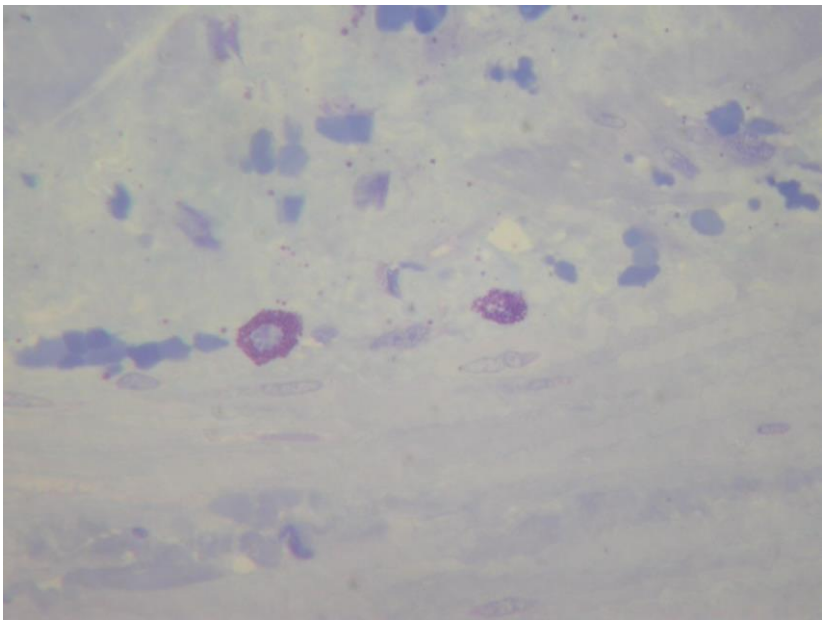
5. Elastic fibres: There were absent in 2 /17 cases, rare in 5 /17 cases, Few in 6/17 cases and Many in 3 /17 cases and inconclusive in 1/17 cases.



Picture 14: Elastic fibres

6. Eosinophil: They are absent in all the cases.
7. Macrophages: Few macrophages were seen in 1/17 cases.

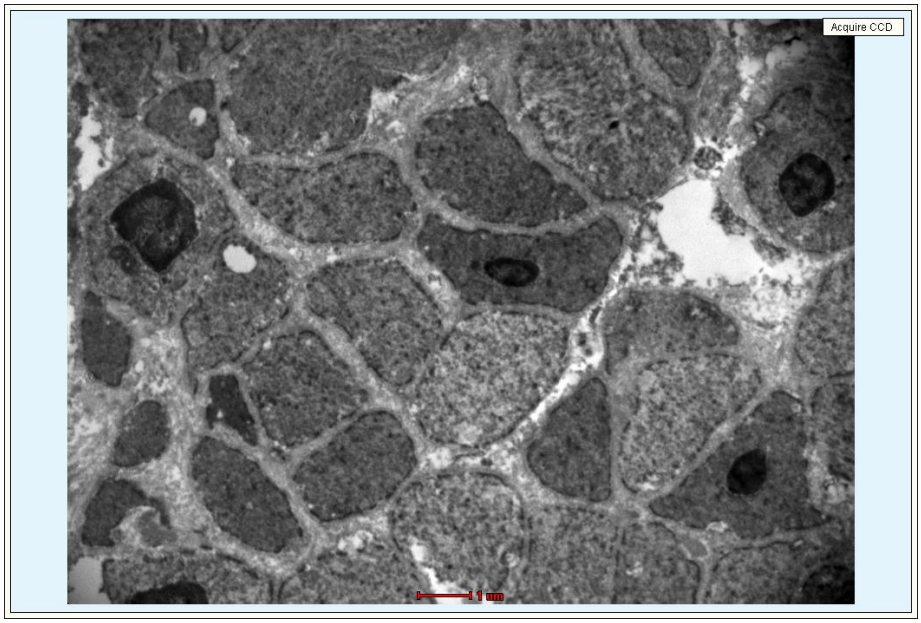
8. Lymphocytes: Few lymphocytes were seen in 1/17 cases.
9. Mast cells: They were absent in 1 /17 cases, rare in 8 /17 cases, few in 4/17 cases and many in 4 /17 cases.



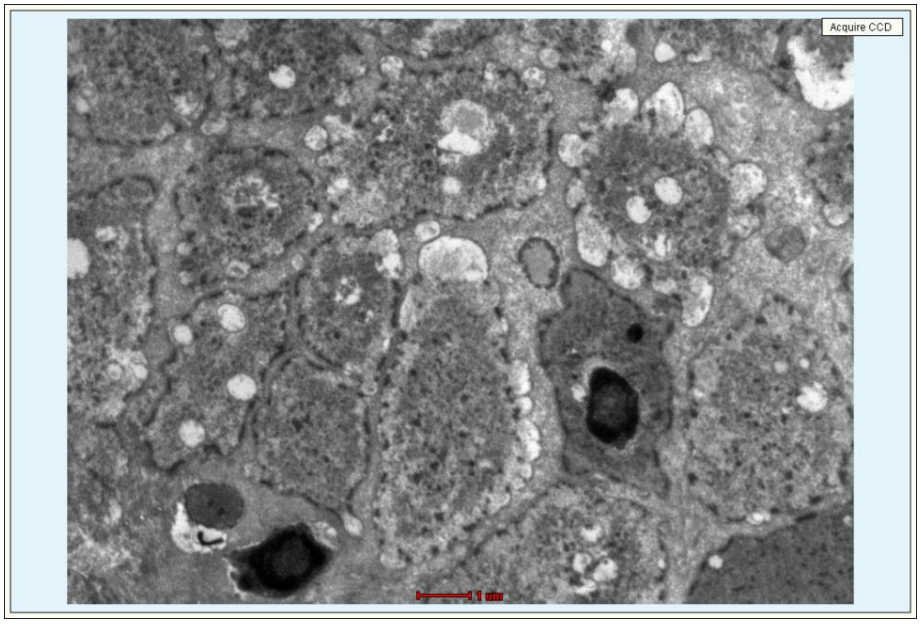
Picture 14: Mast cells

Electron microscopy :

1. Fibrosis of the peri-muscular connective tissue was noted.

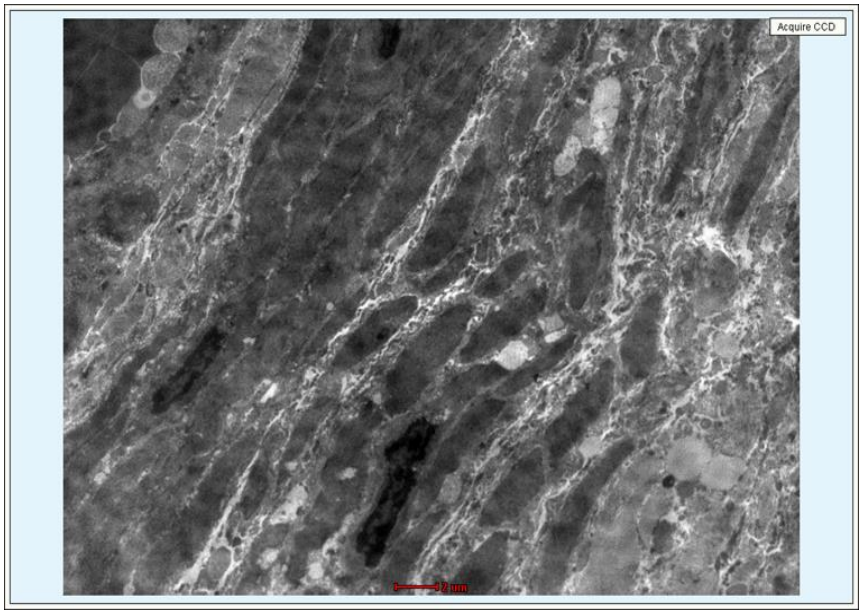


Picture 15A: Fibrosis in the perimucular connective tissue of the esophagus smooth muscle

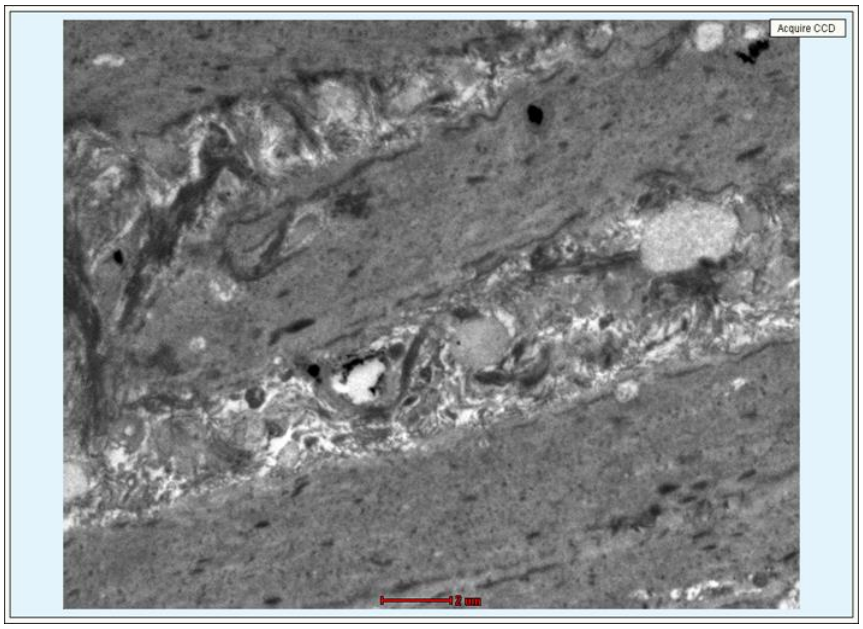


Picture 15B : Fibrosis in the perimuscular connectiv tissue at the lower esophageal sphincter.

2. Fibrosis of muscle fibres were noted.

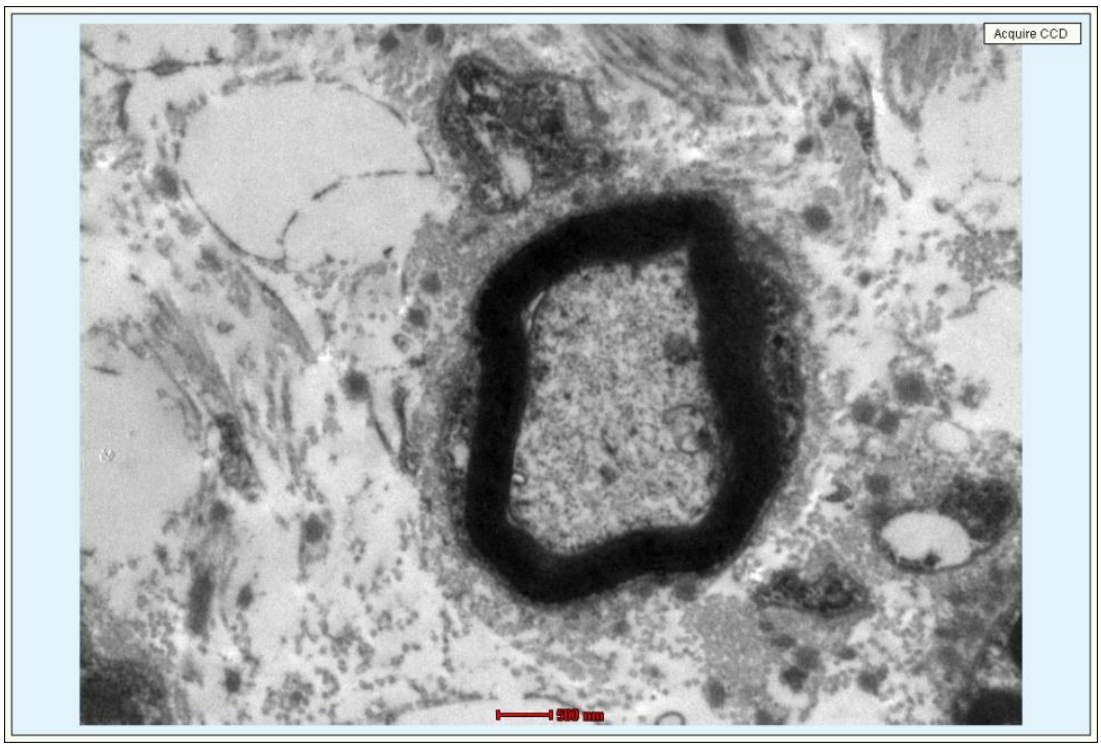


Picture 16A: Fibrosis of muscle layer - Mild

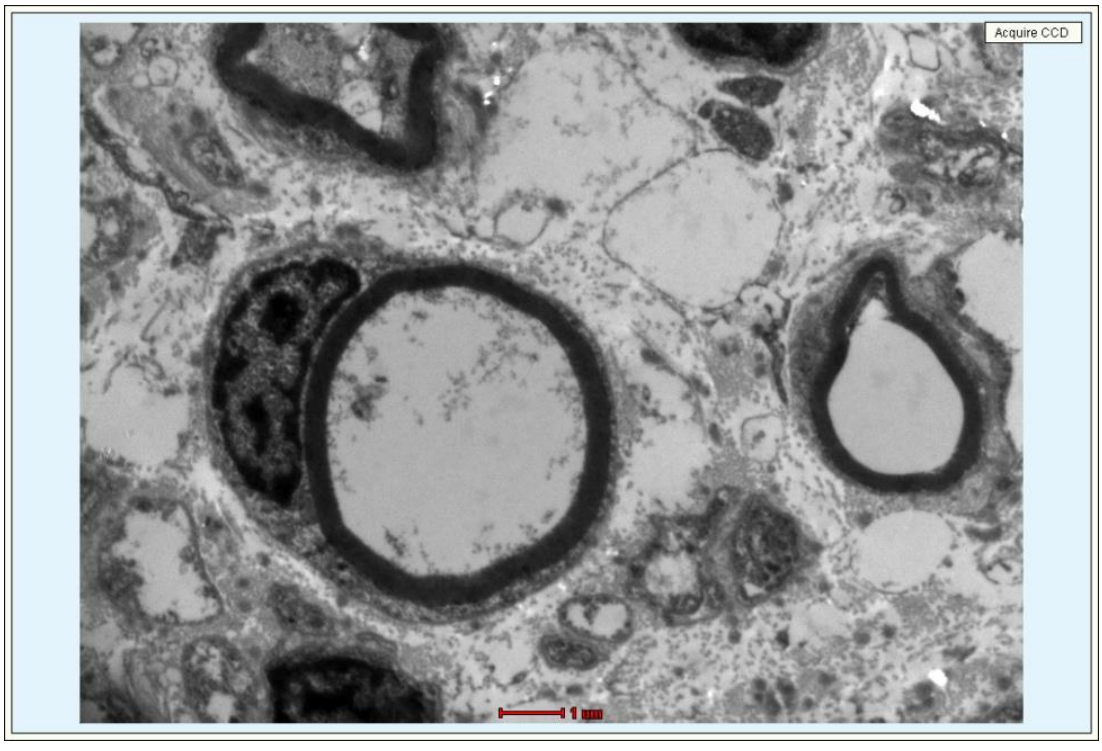


Picture 16B : Fibrosis of muscle layer - Severe

3. Demyelination of the nerve bundles were noted suggesting primary neuronal injury.

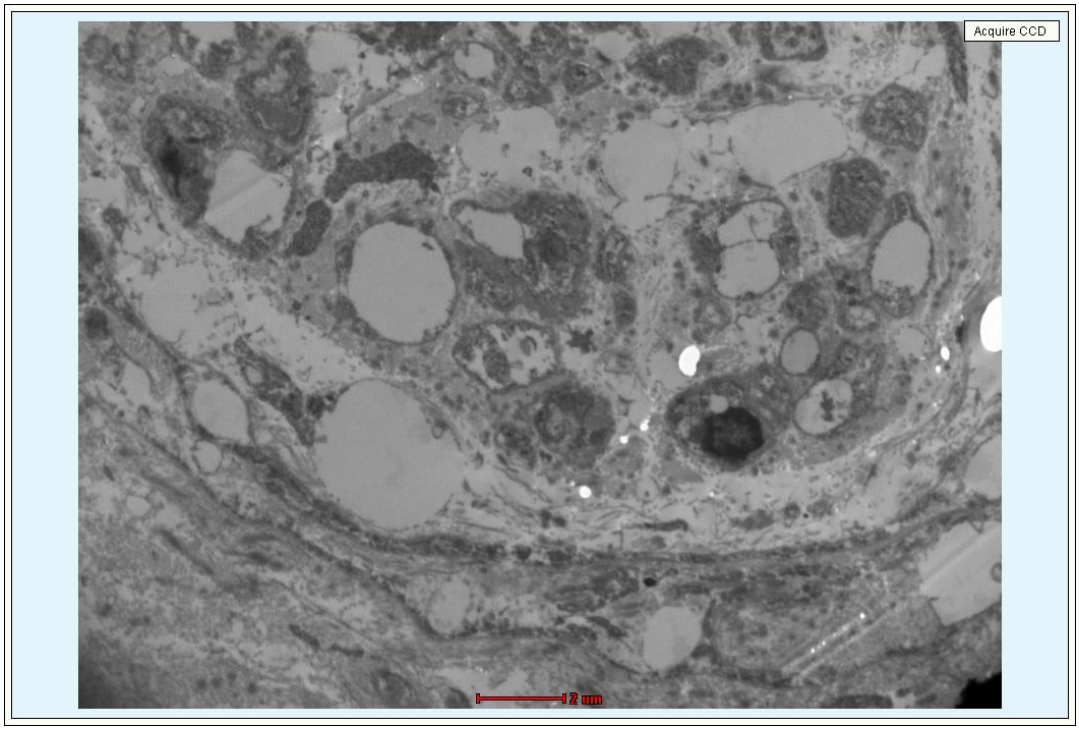


Picture 17A : Normal myelinated nerve

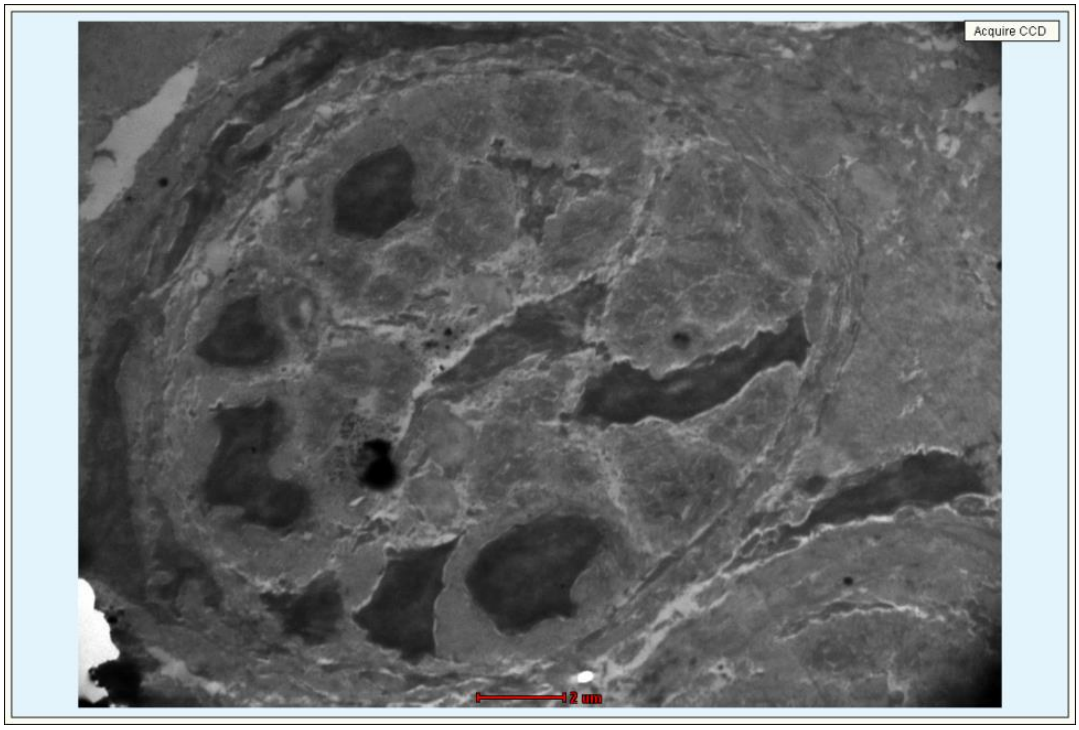


Picture 17B : Demyelinated nerve fibre

4. Degenerated pre-ganglionic and post-ganglionic nerve fibres.

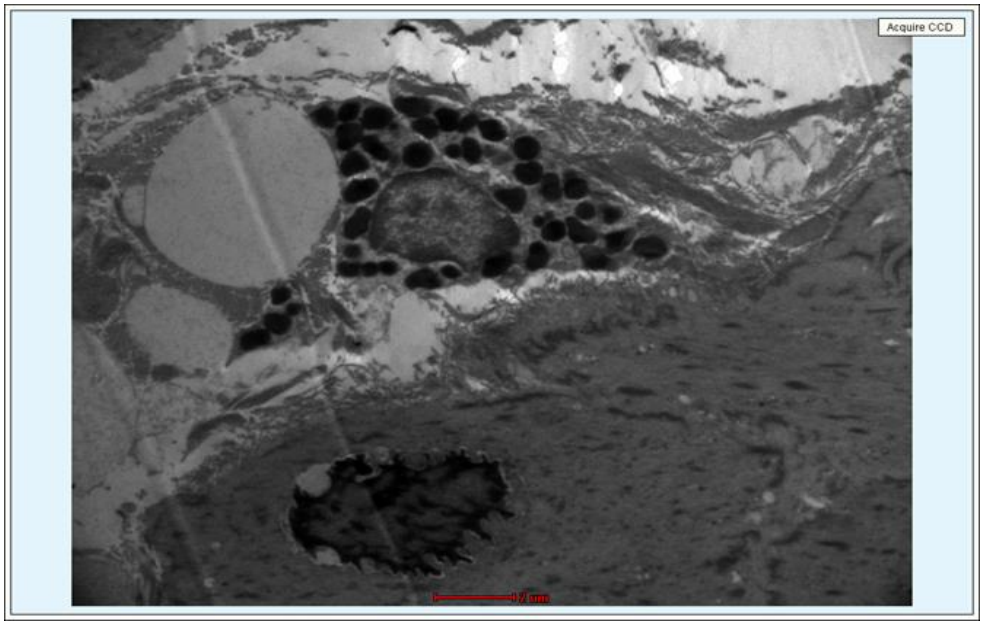


Picture 18A: Degenerated of pre-ganglionic nerve fibres



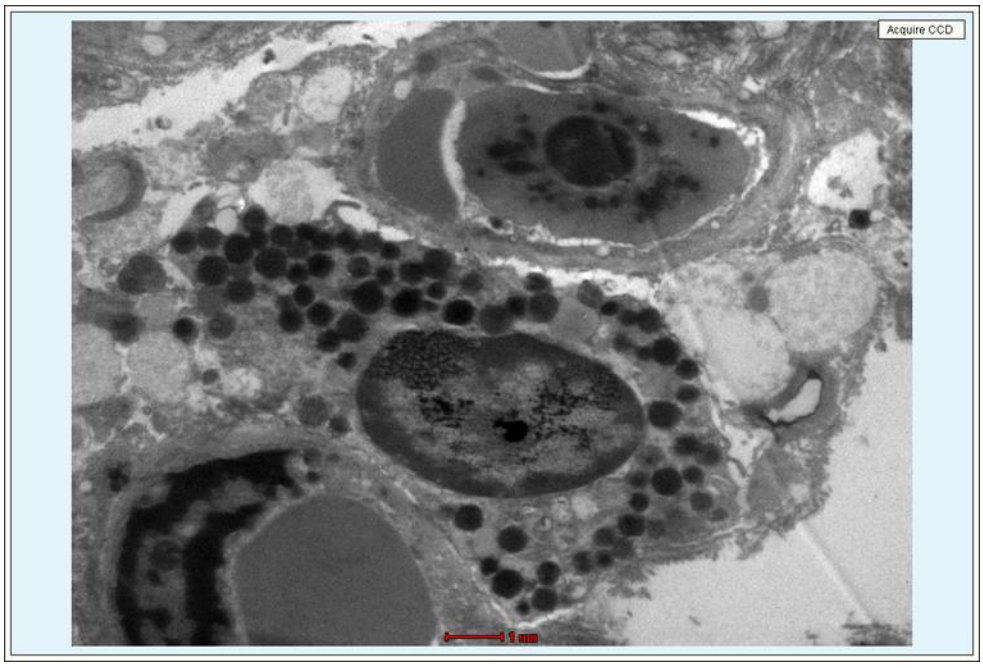
Picture 18B: Degenerated of post-ganglionic nerve fibres

5. Eosinophils were noted



Picture 19: Eosinophils

6. Mast cells were noted

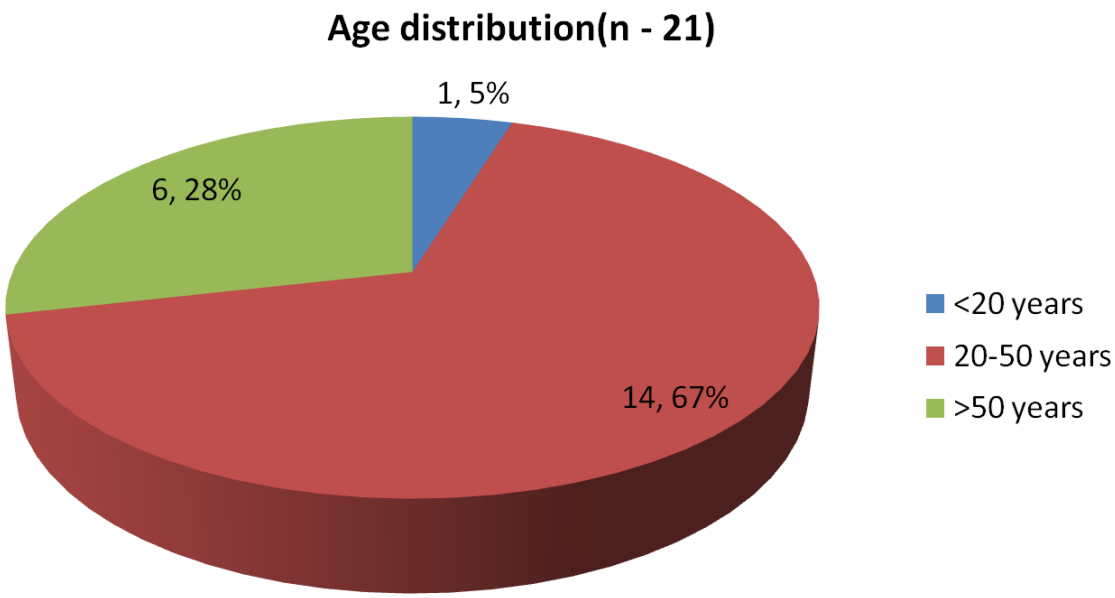


Picture 20: Mast cells.

Demography and other clinical results

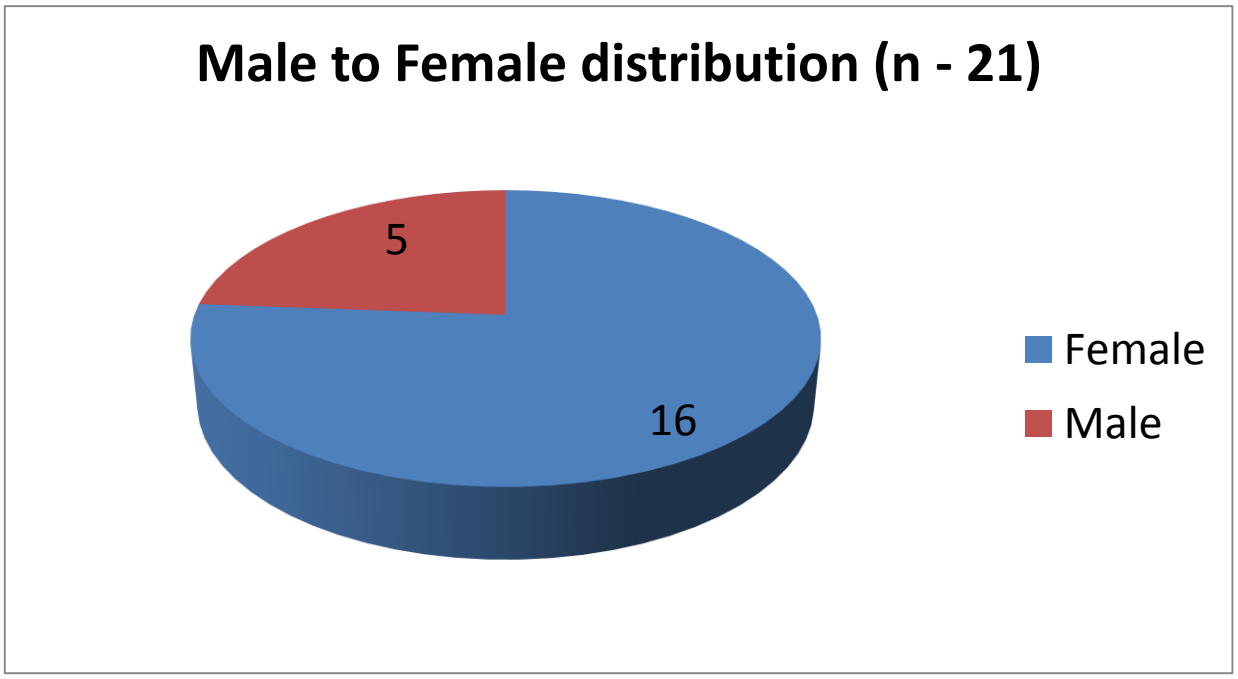
Age distribution:

The patients were divided into three groups according to age. Achalasia was noted commonly in the 20 to 50 age group. The disease can occur in age group but onset before adolescence is rare.



Male to female distribution:

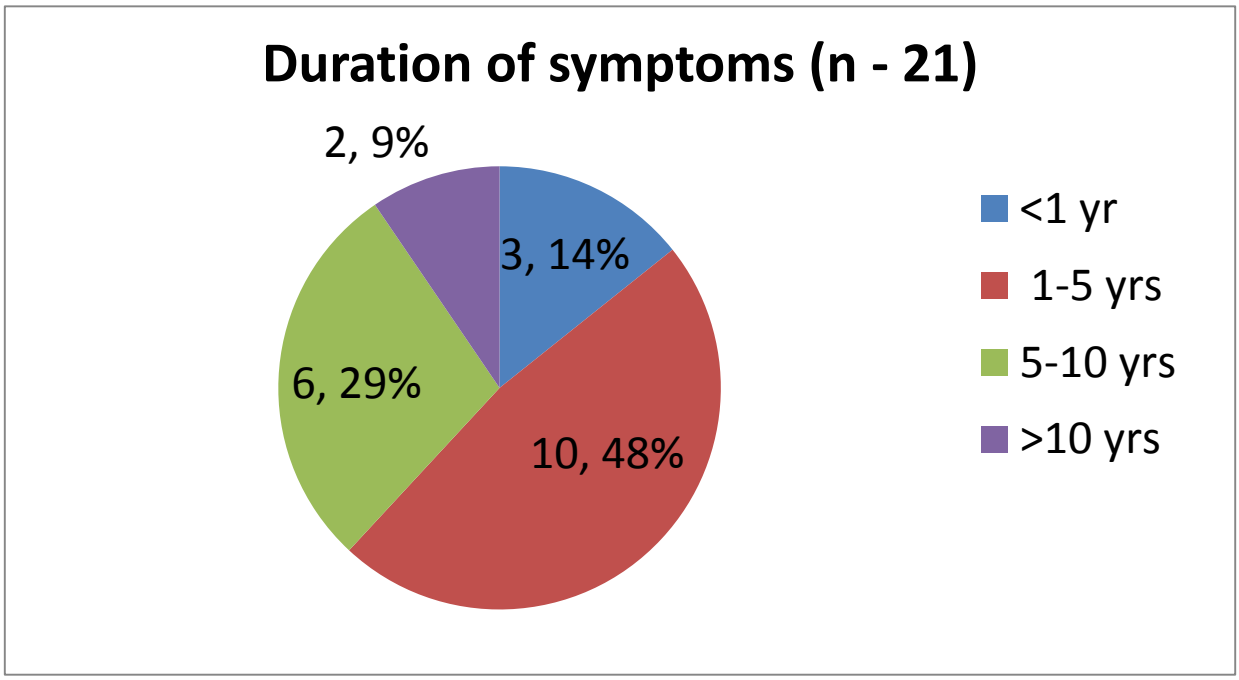
It was noted to be more common in females though in many studies they were noted to be equal in both genders.



Duration of symptoms:

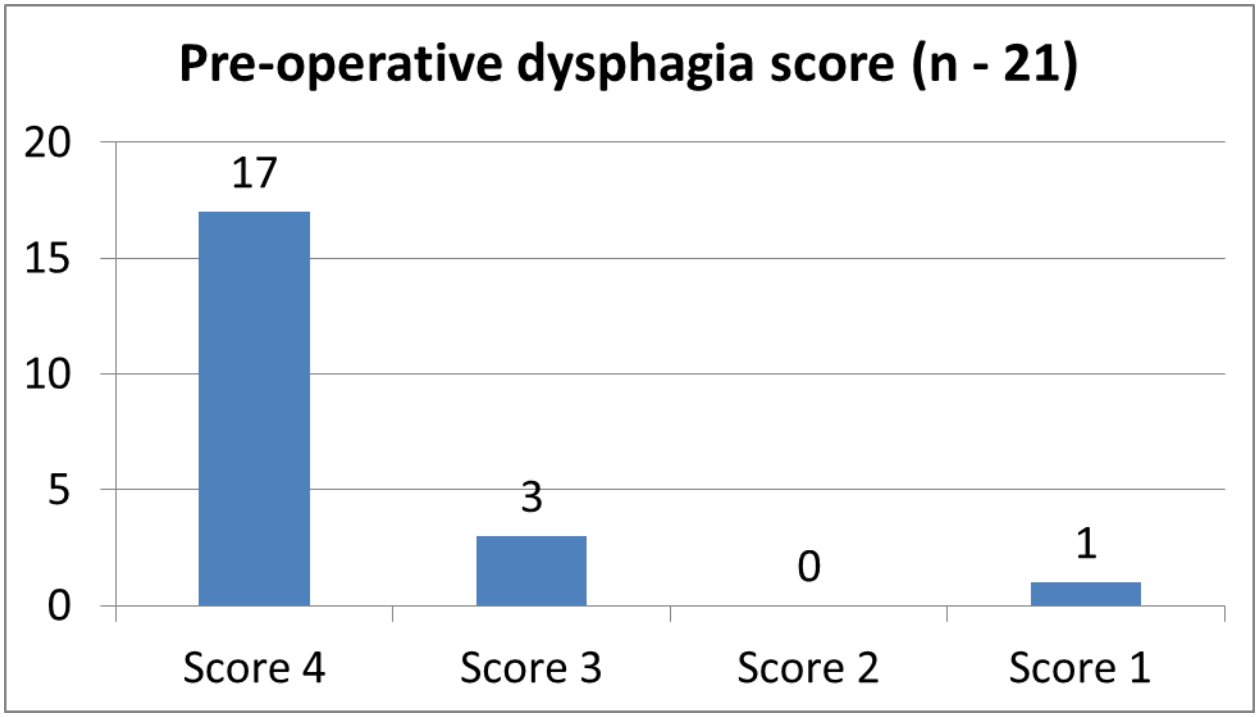
Approximately 50% of the patients presented with 5 years of onset of symptoms.

Earliest was at 4 months duration and longest was 15 years duration of illness.



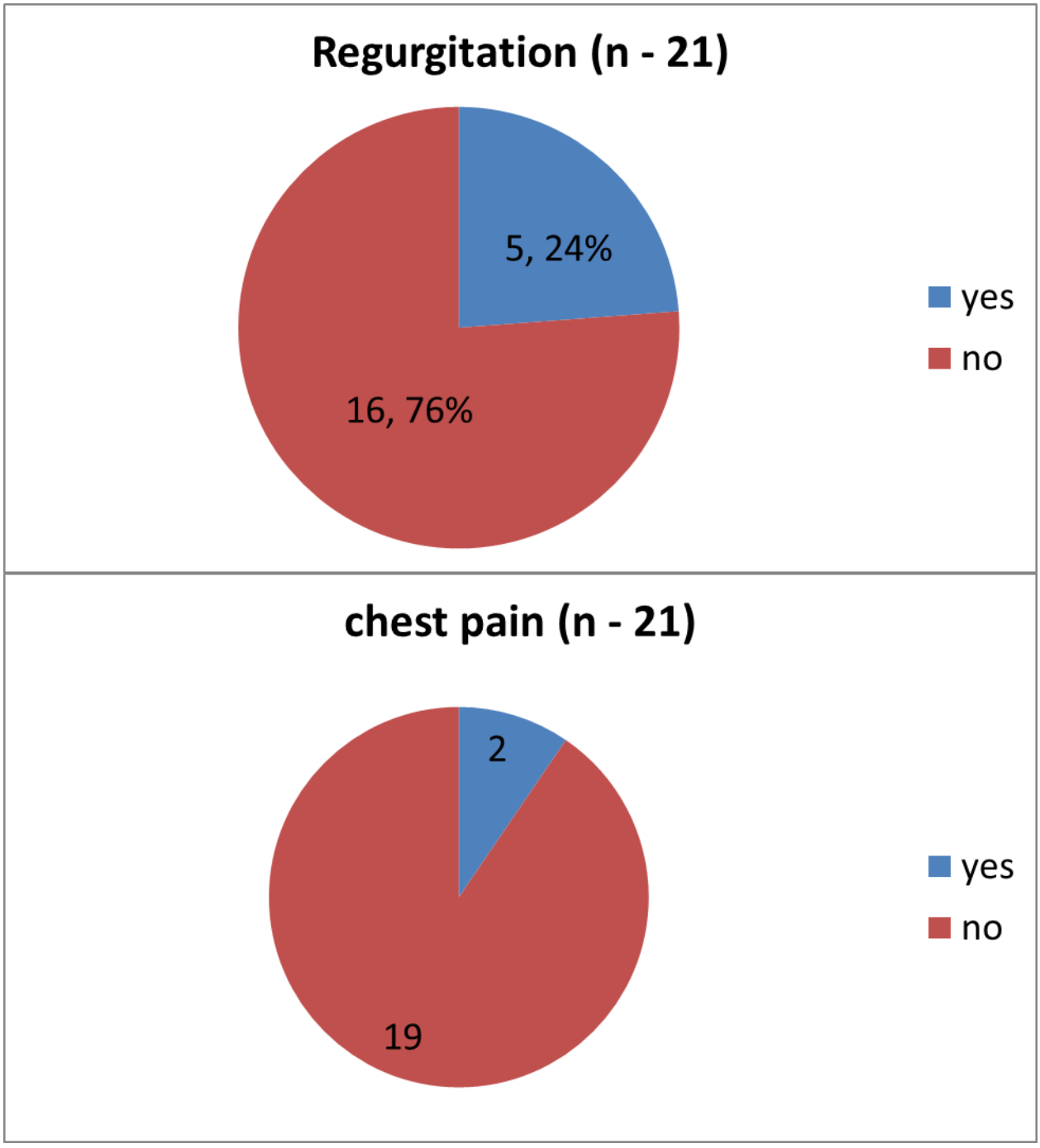
Dysphagia score:

Mellows and Pinhas scoring system. Majority of the patients had dysphagia score of 4.



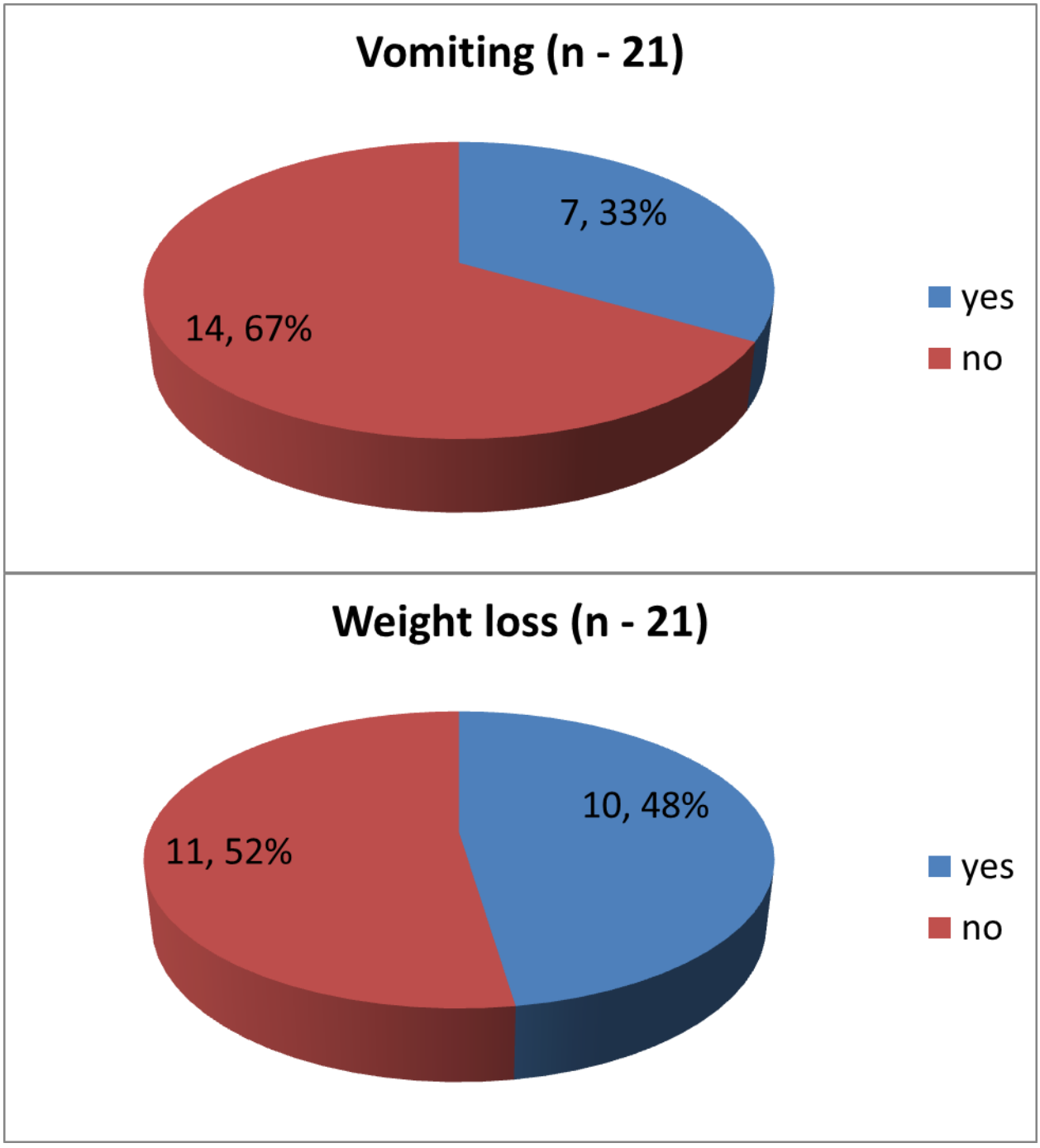
Regurgitation and chest pain:

Majority of the patients did not have regurgitation. Only a minority of them had chest pain



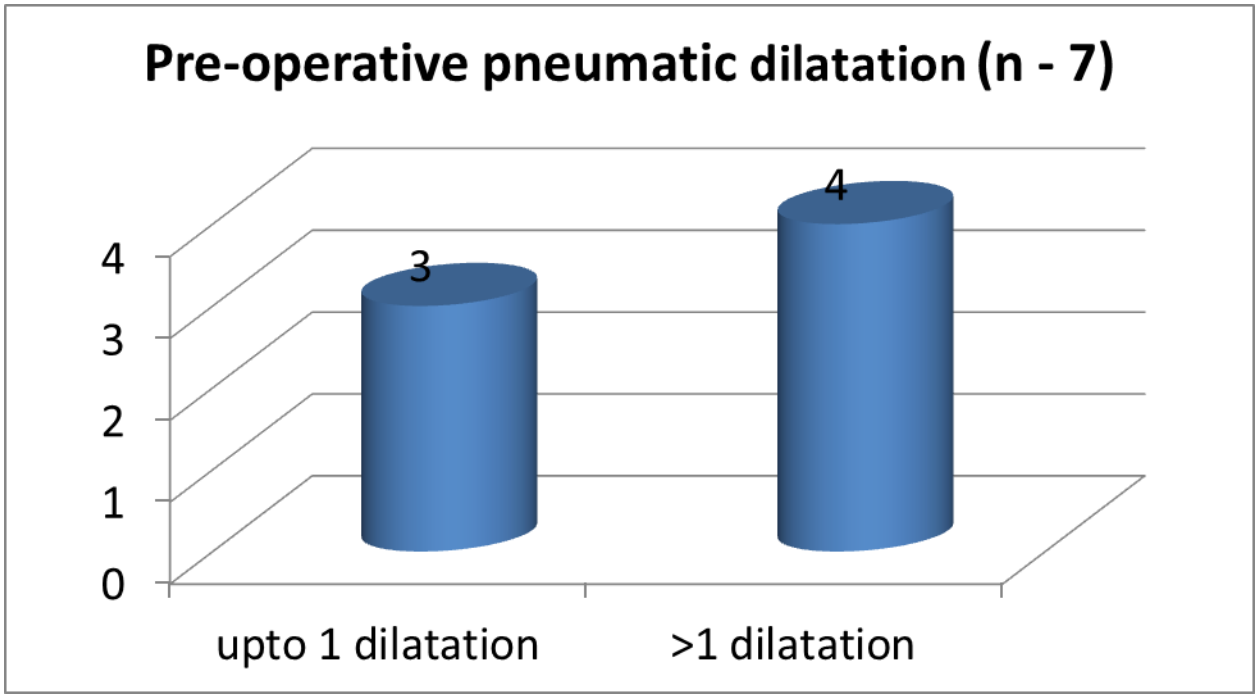
Vomiting and weight loss:

Vomiting was noted in many of our patients. Weight loss is noted in approximately half of them.



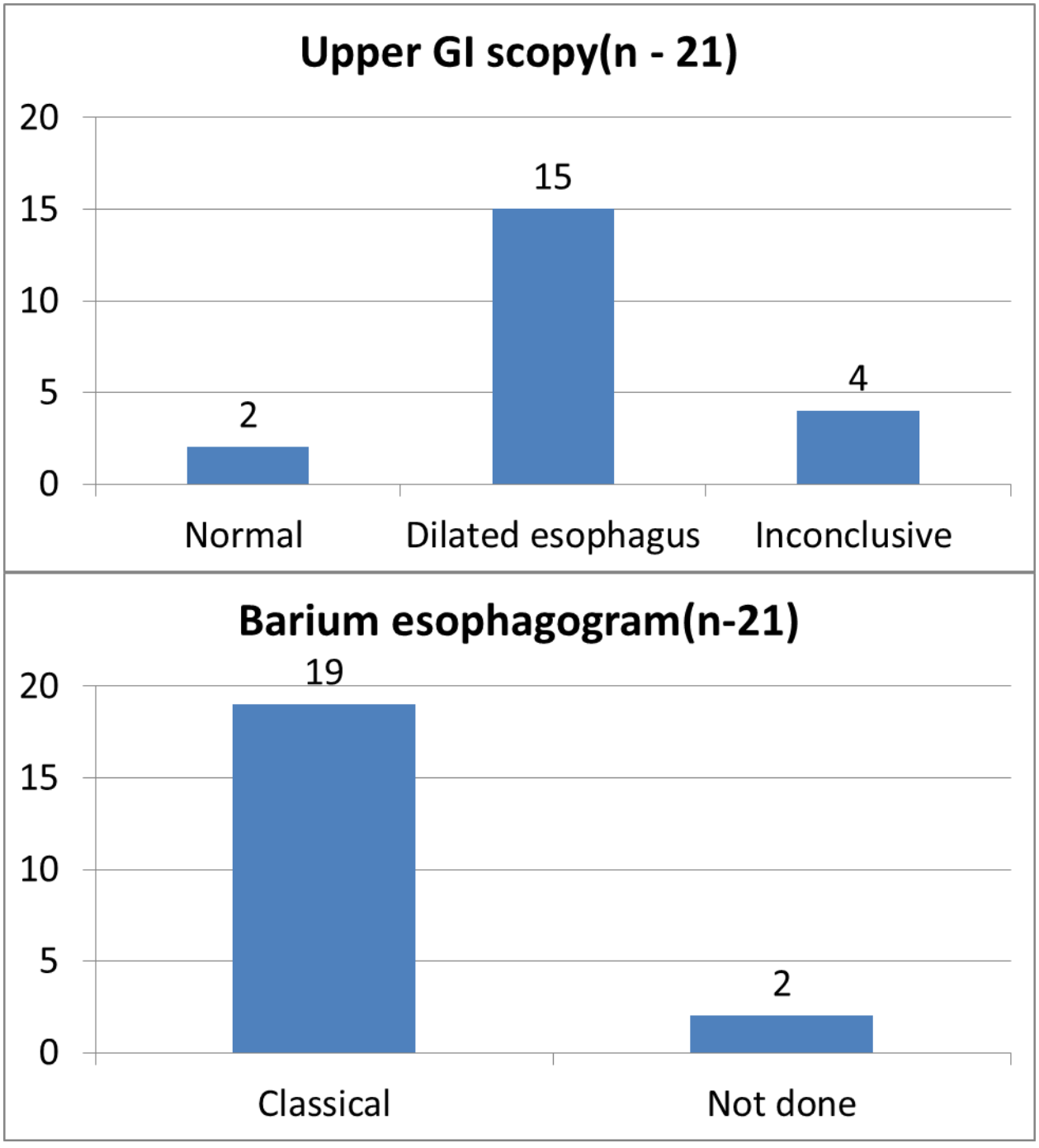
Pre-operative pneumatic dilatation:

Seven of our patients had undergone balloon dilatation and 4 patients had undergone multiple dilatations.



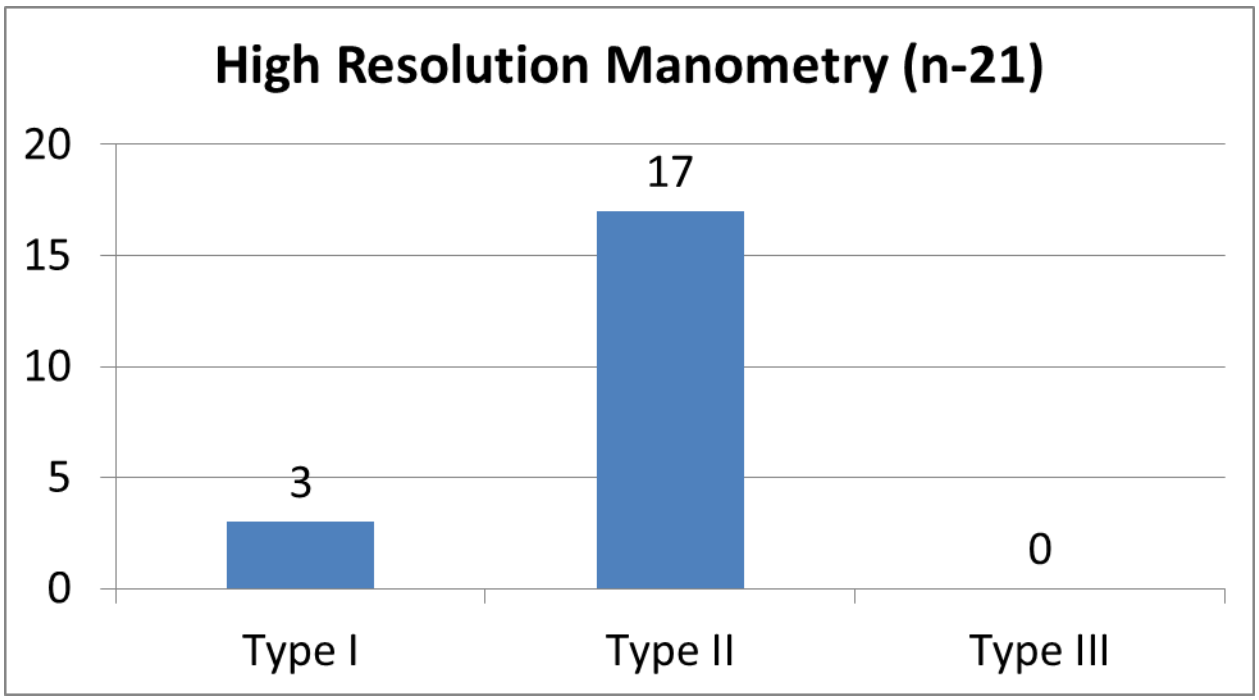
Upper GI scopy and Barium esophagogram:

Upper GI scopy was done in all the patients. Barium esophagogram is done in majority of the patients.



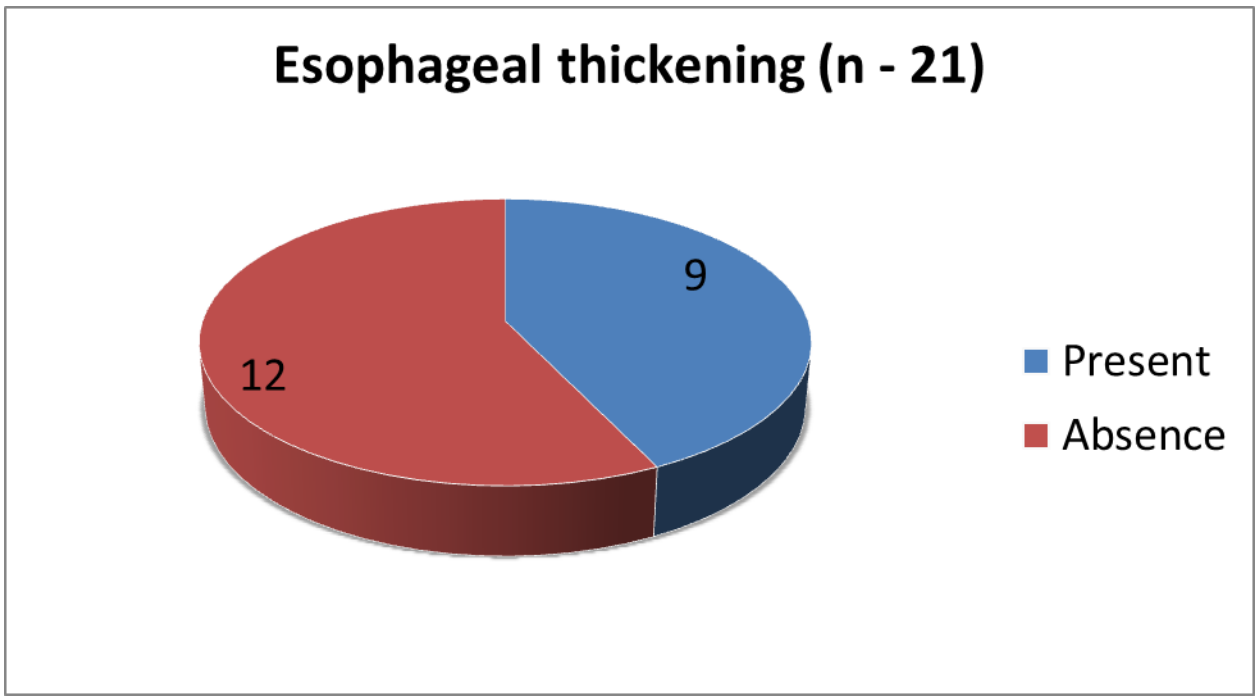
High resolution manometry:

Manometry was done in twenty patients. Except in one patient who had a megaesophagus. There were also logistic reasons for not being able to get the test done.



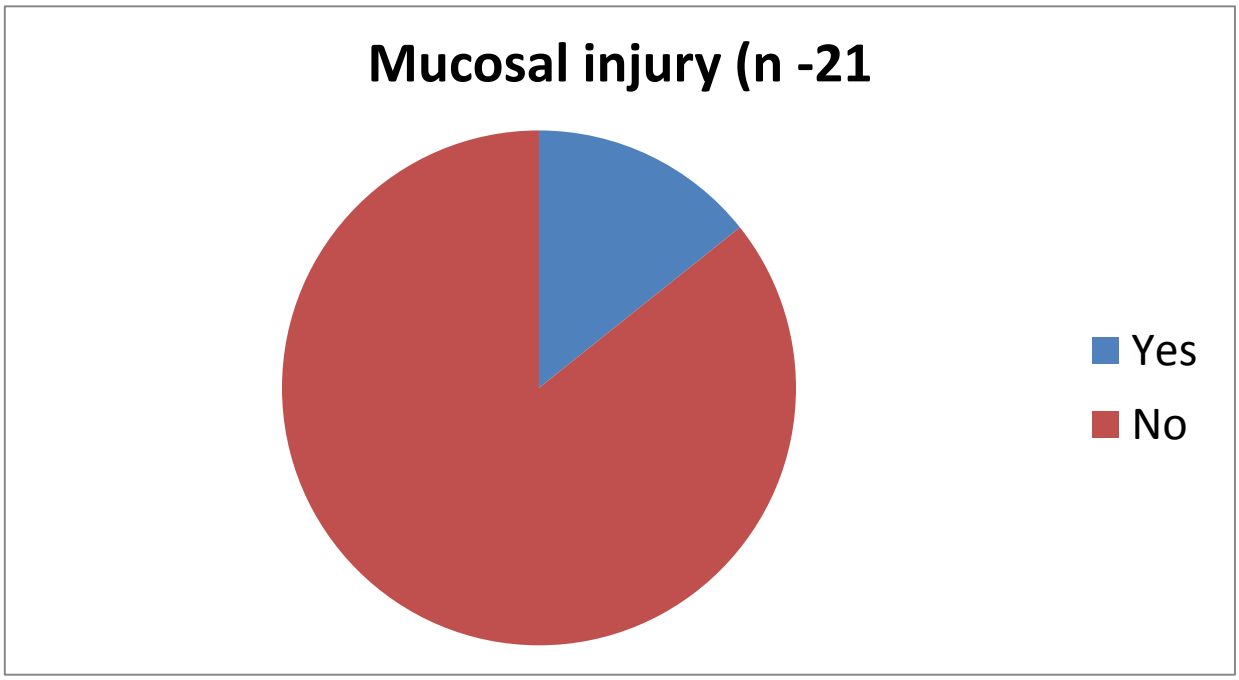
Intra-operative data

Esophageal thickness:



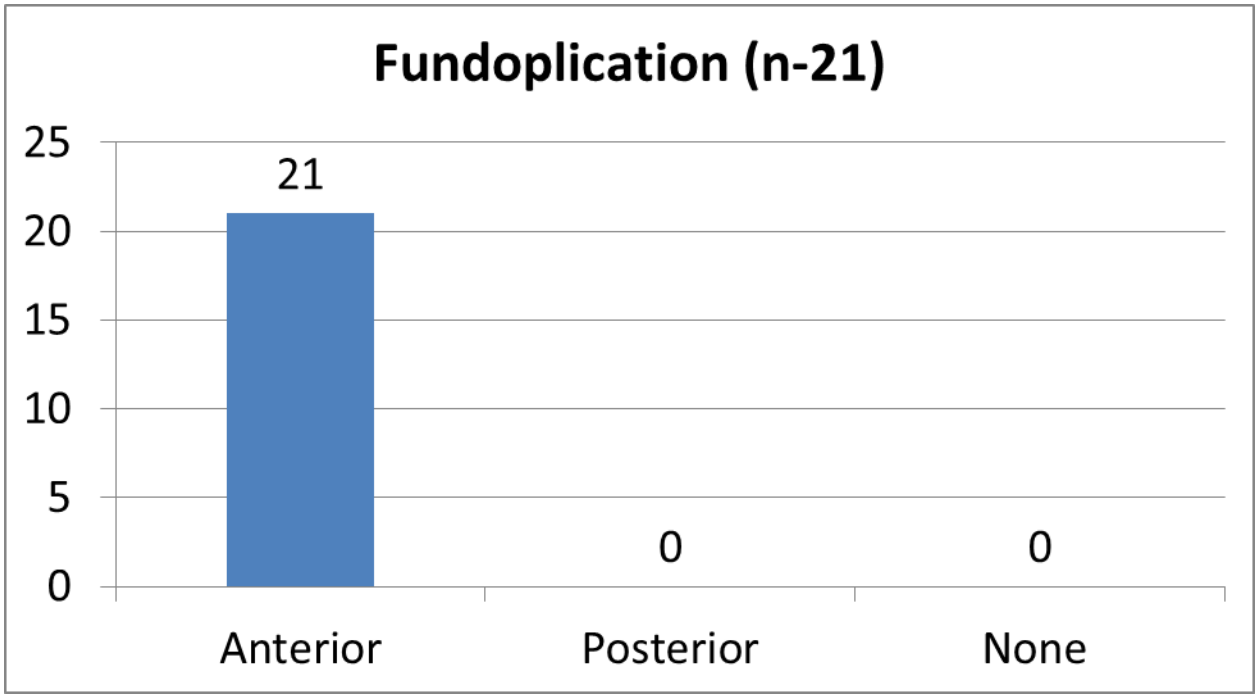
Mucosal injury:

Mucosal injury was encountered in three patients and it was repaired primarily. Leak test was not done routinely for all patients.



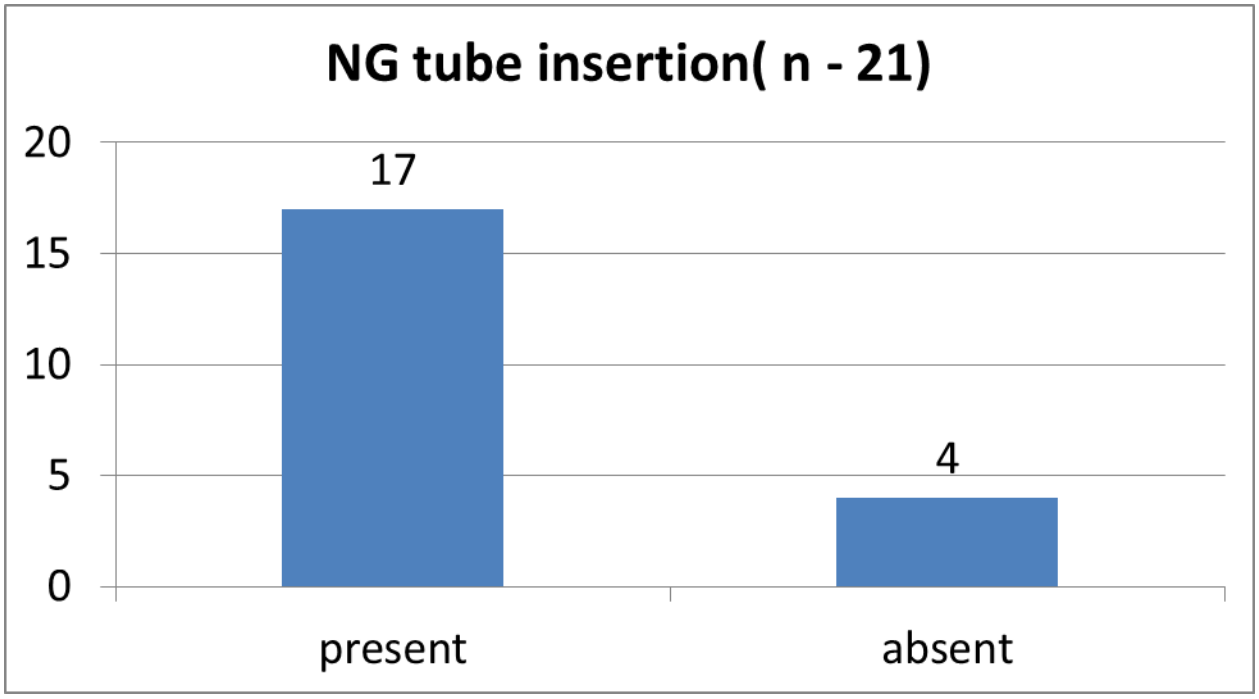
Fundoplication:

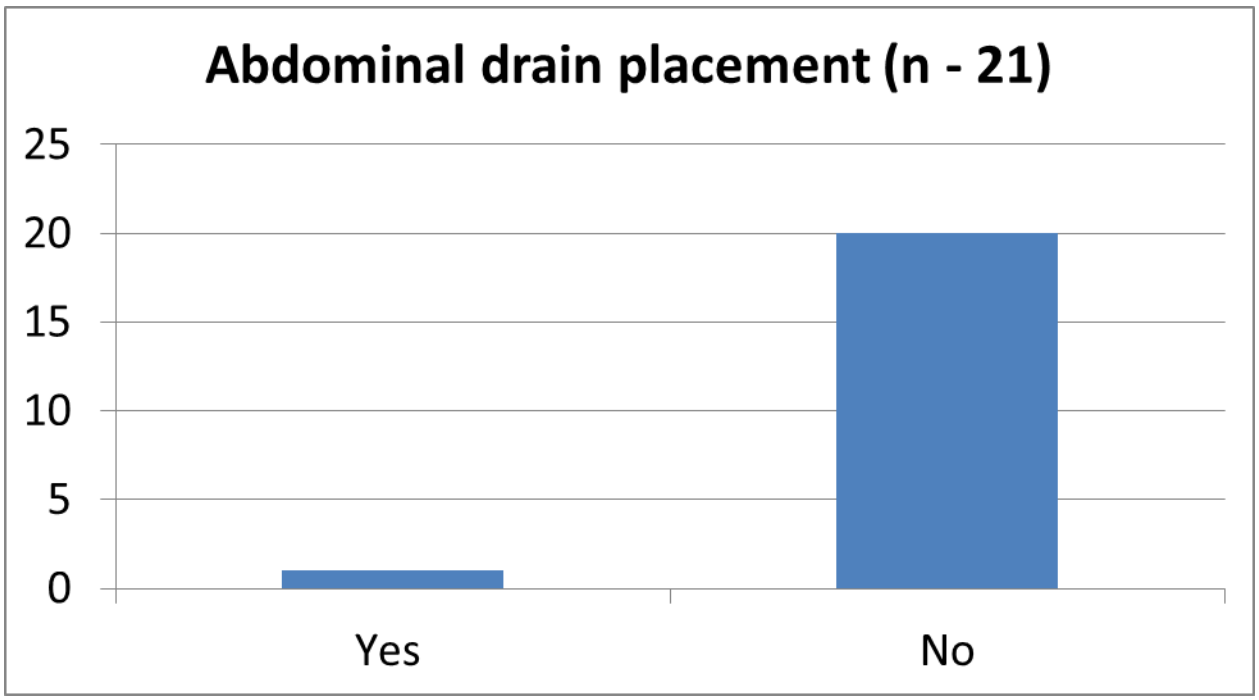
All the patients underwent anterior Dor's fundoplication.



NG tube and abdominal drain placement:

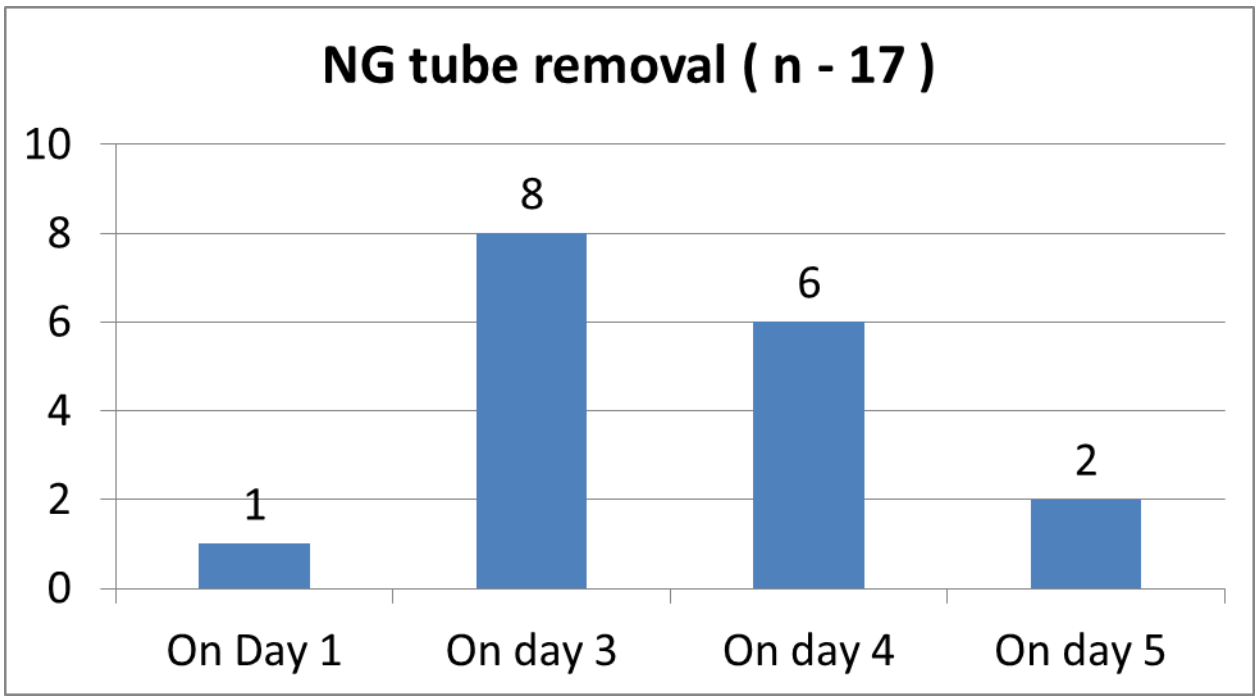
Seventeen patients underwent nasogastric tube placement.

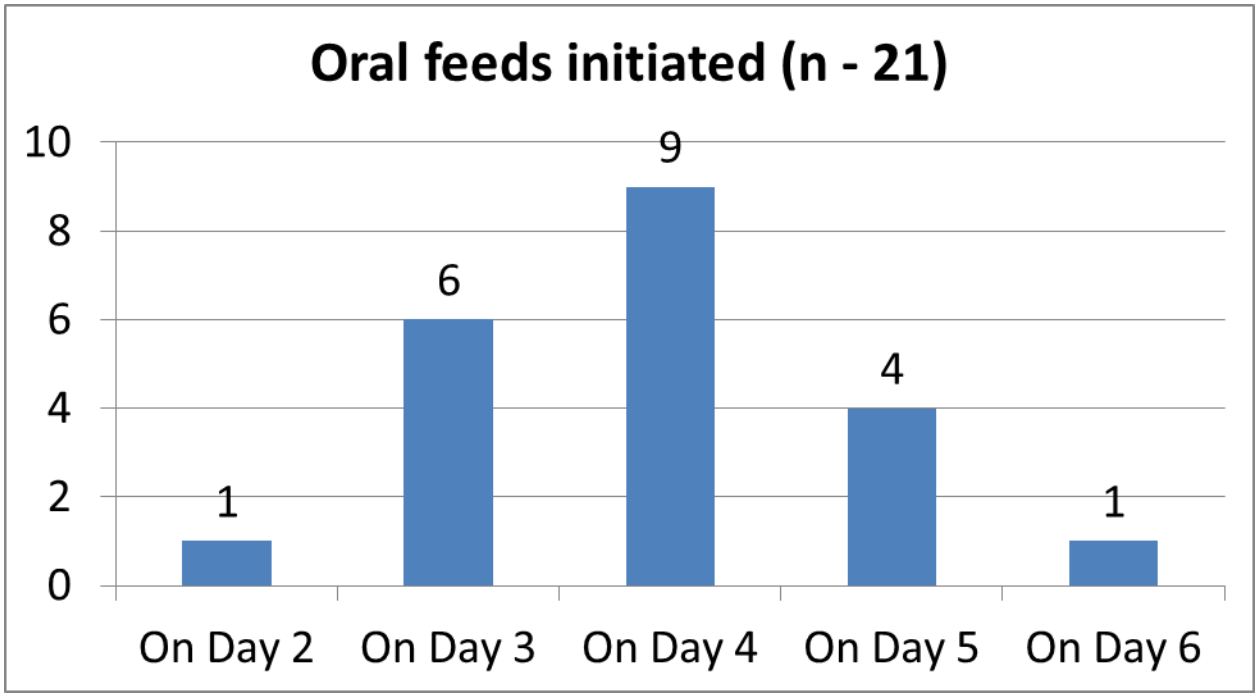




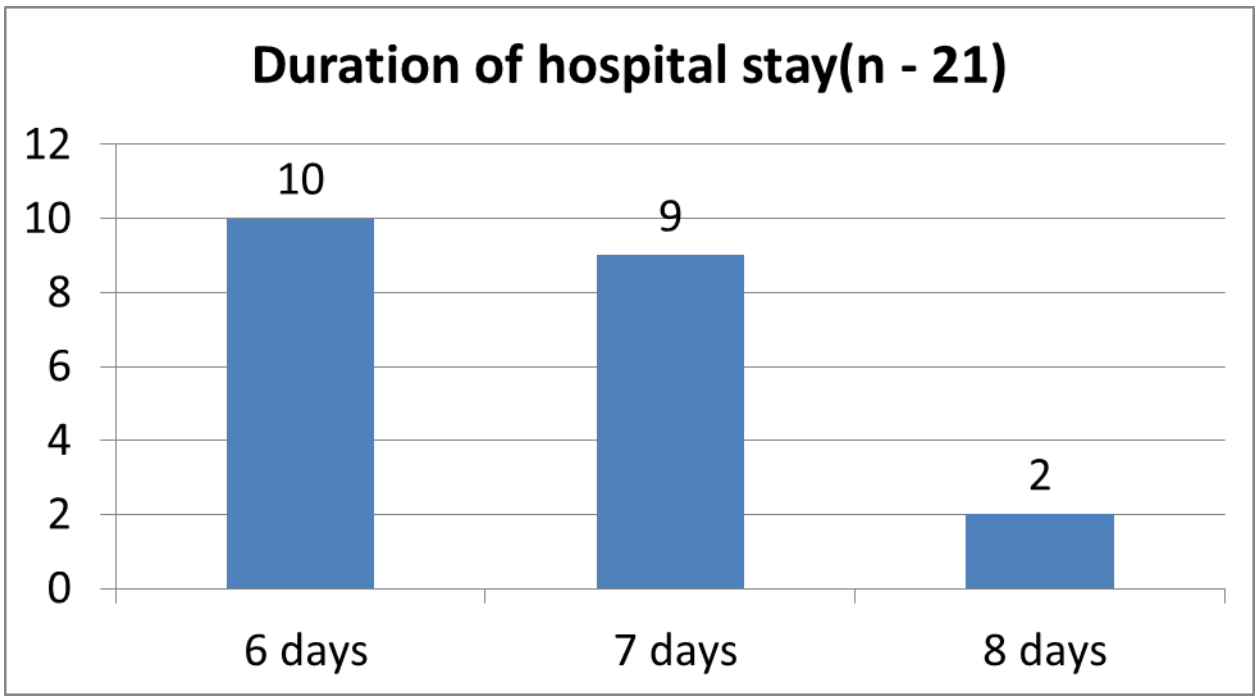
Post-operative data :

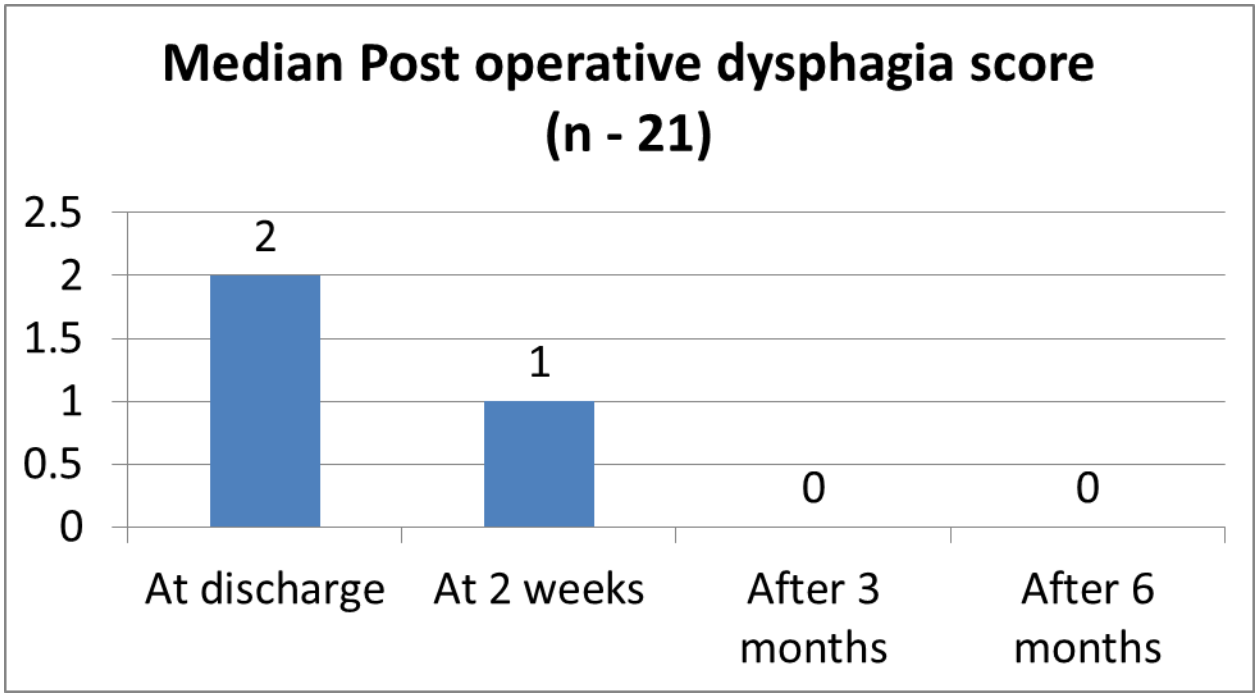
NG tube removal and initiation of feeds





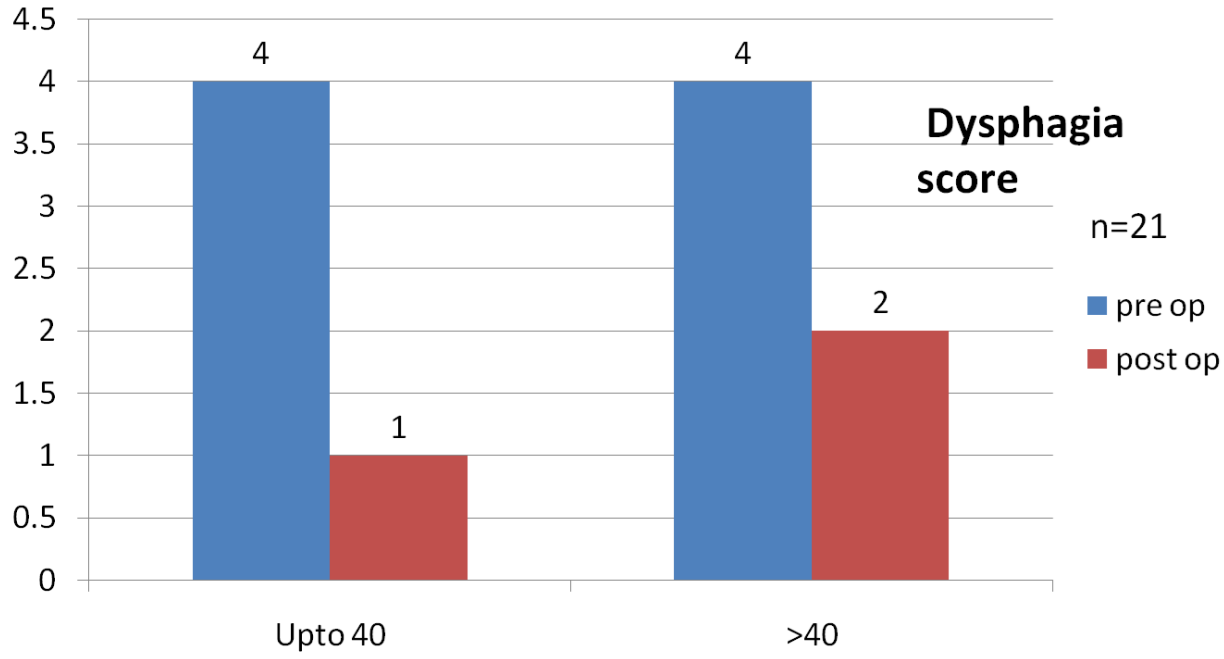
Duration of hospital stay and post-operative dysphagia score:



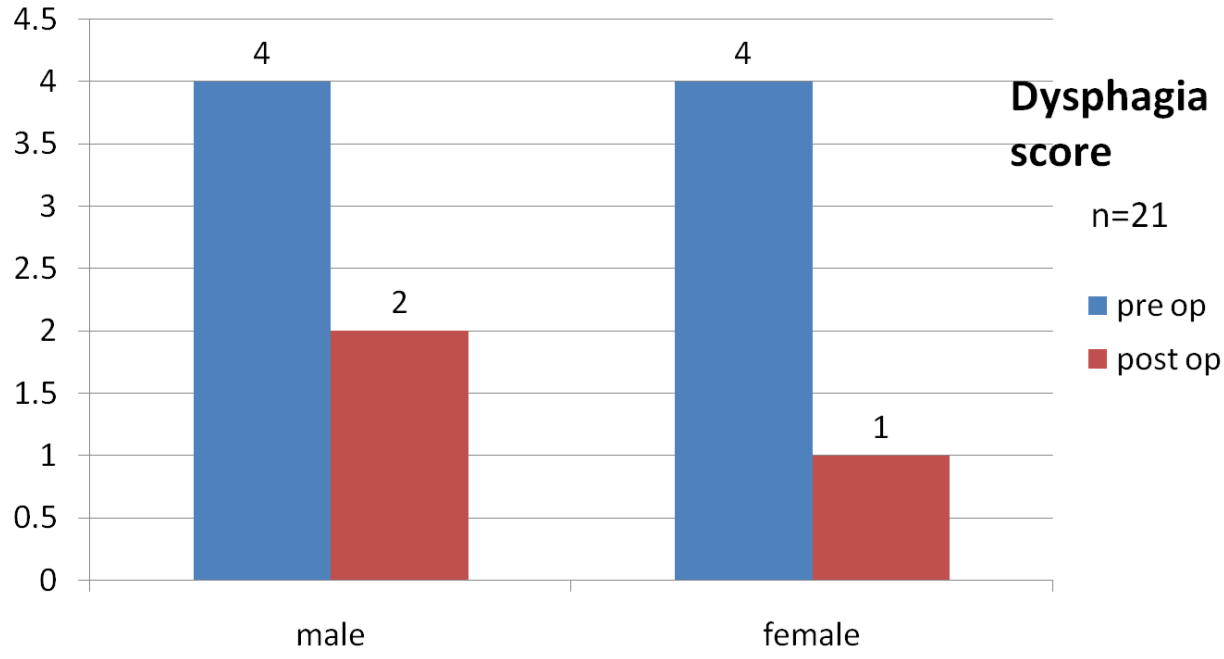


Comparative analysis:

Post-operative dysphagia score vs. age and sex

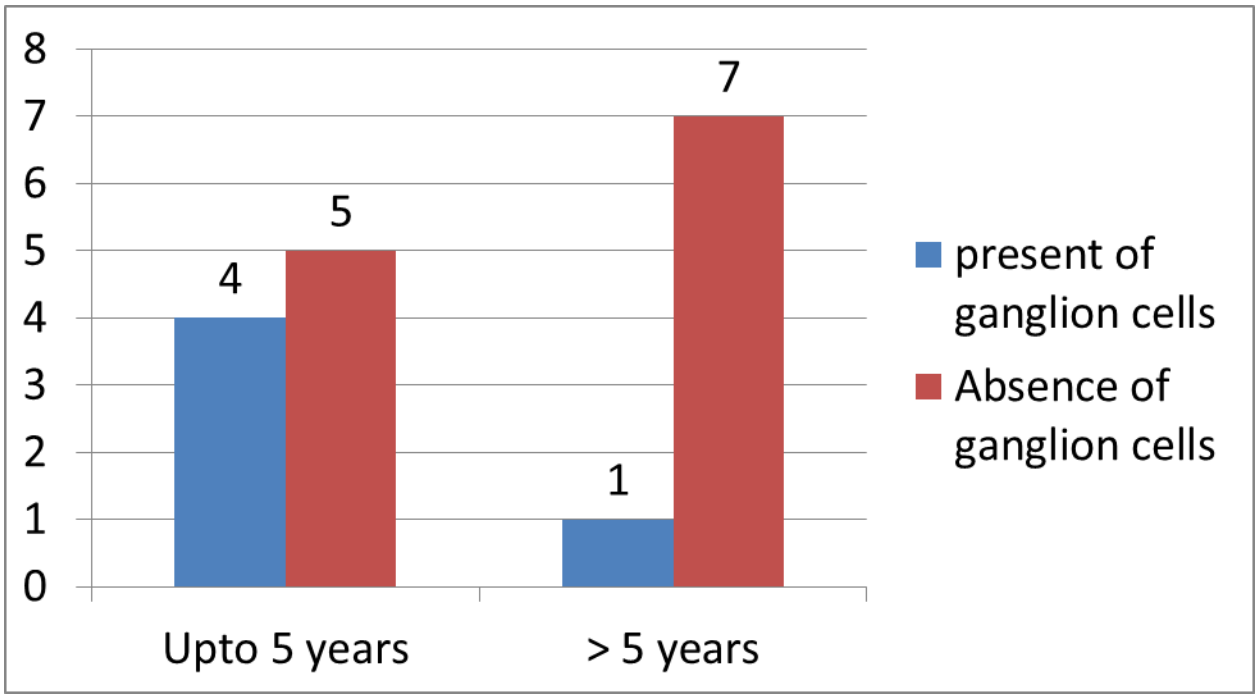


It is clear that the patient with age less than 40 had better post-operative relief of dysphagia and women have better relief than men after the operation.

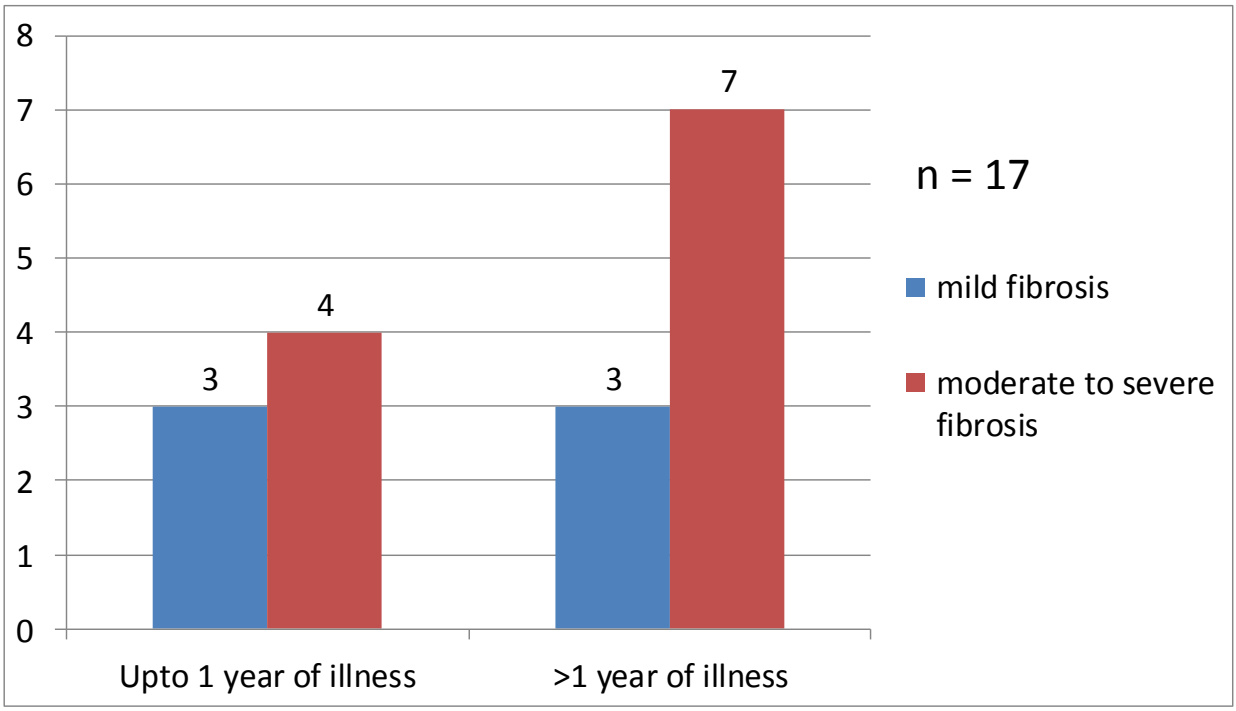


Duration of illness vs. ganglion cells and fibrosis:

Ganglion cells decreases with increasing duration of illness

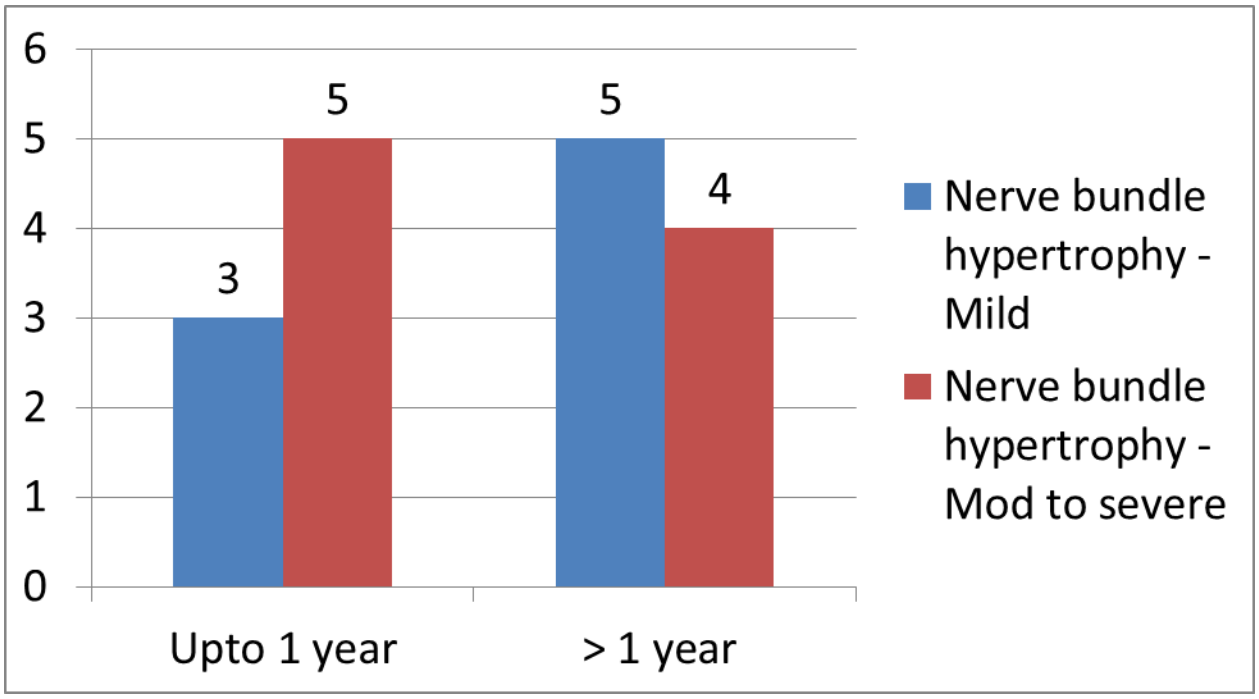


Similarly, histopathological evidence of Fibrosis was noted to be increasing with prolonged duration of illness, of more than one year.

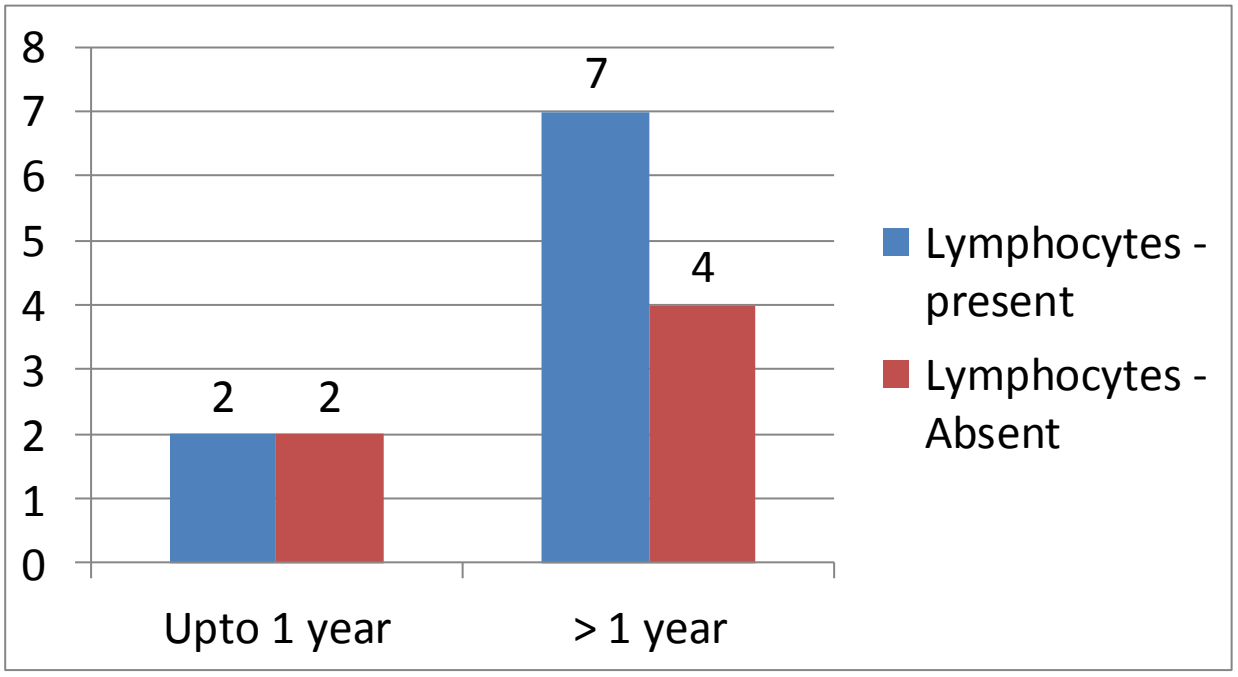


Duration of illness vs. inflammation and nerve bundle hypertrophy:

There is no difference in nerve bundle hypertrophy with duration of illness. (n - 15)

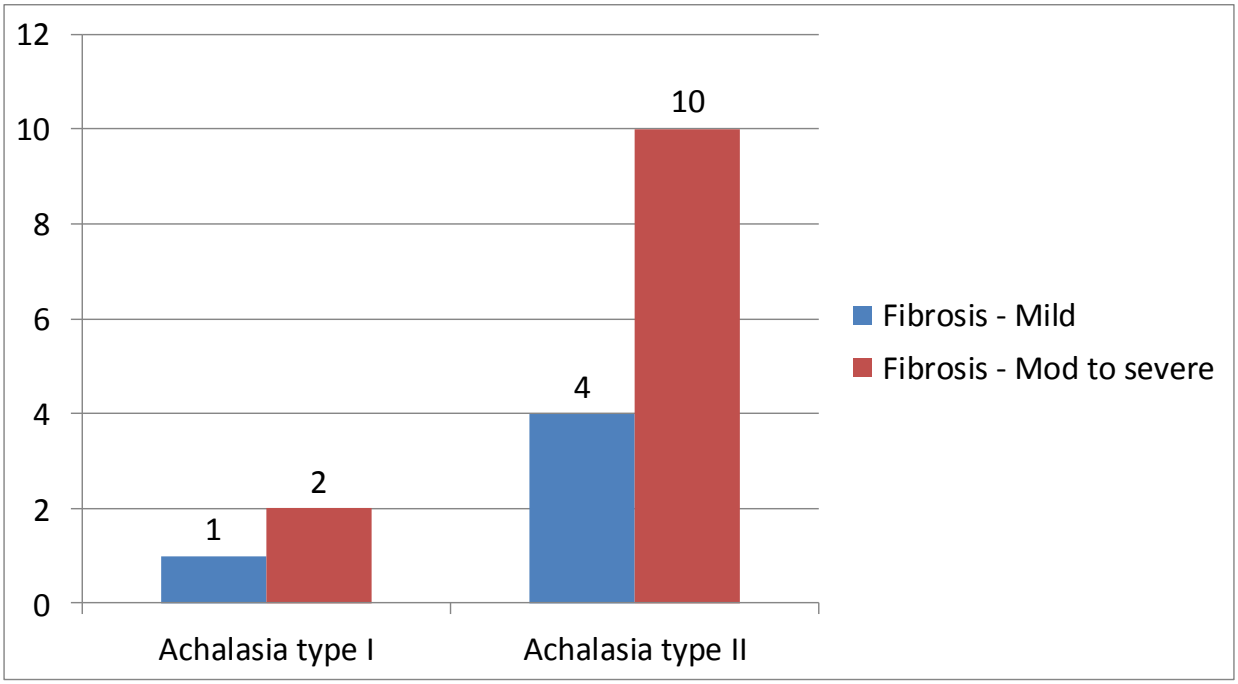


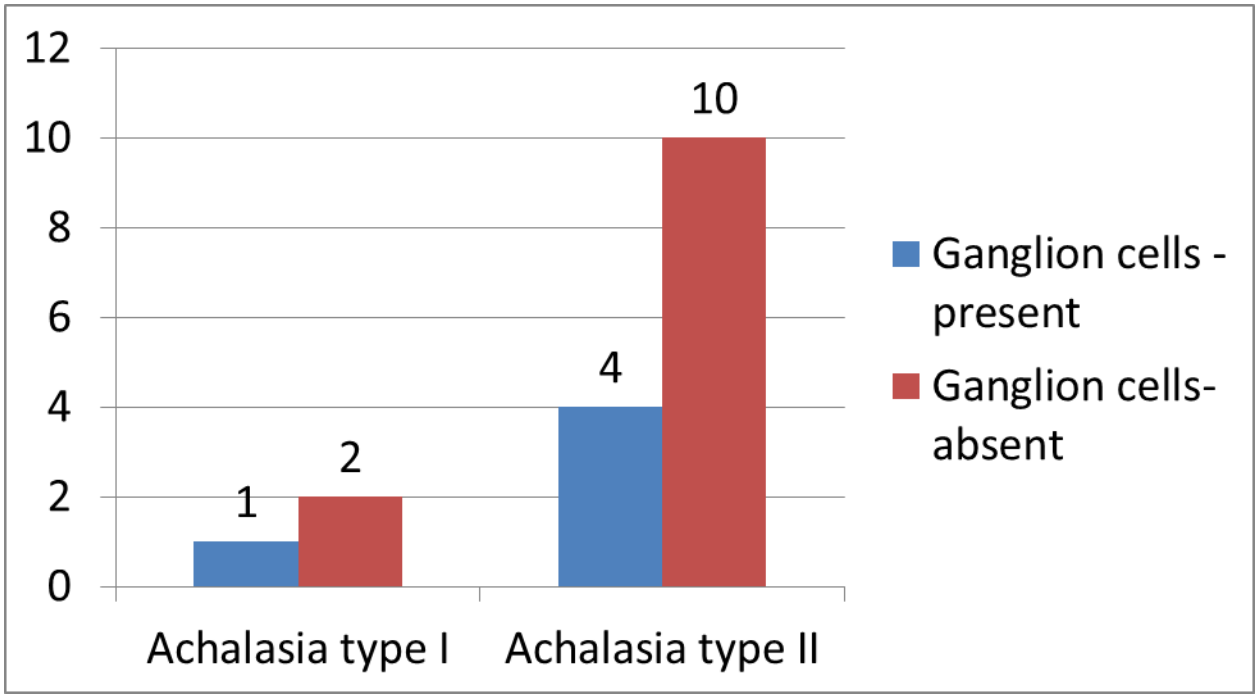
There was no difference in the presence of inflammatory cells with durarion(n-15)



Type of achalasia and fibrosis:

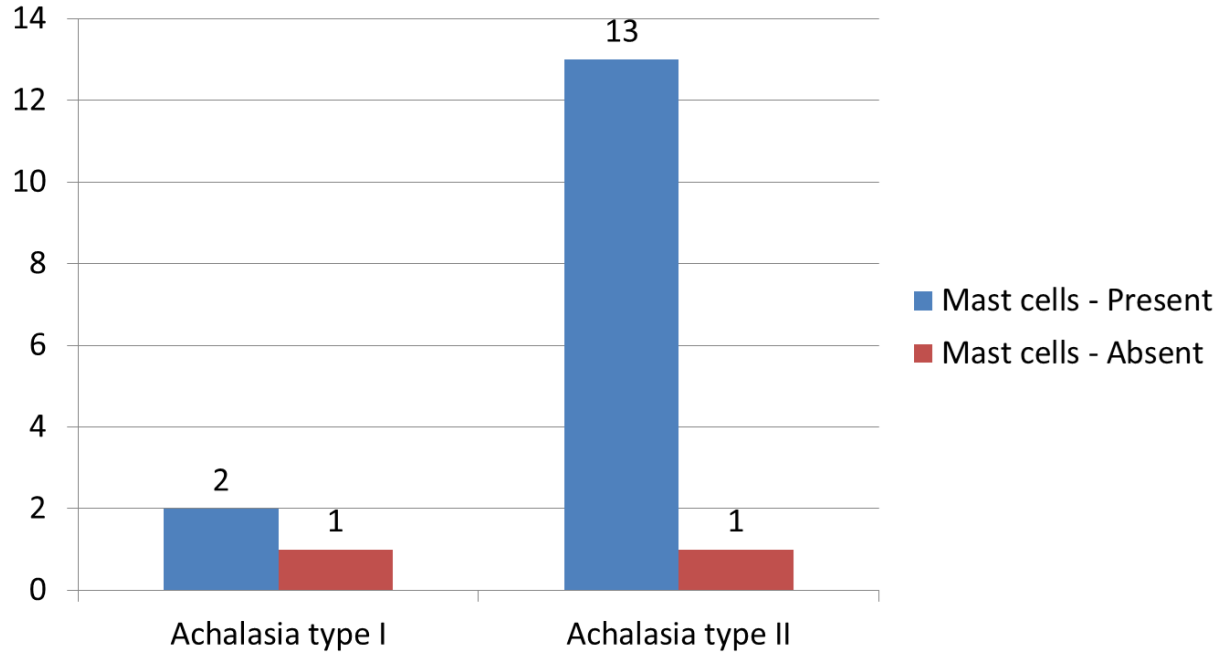
The extent of fibrosis and the density of ganglion cells did not show any variation in the two manometric types of Achalasia



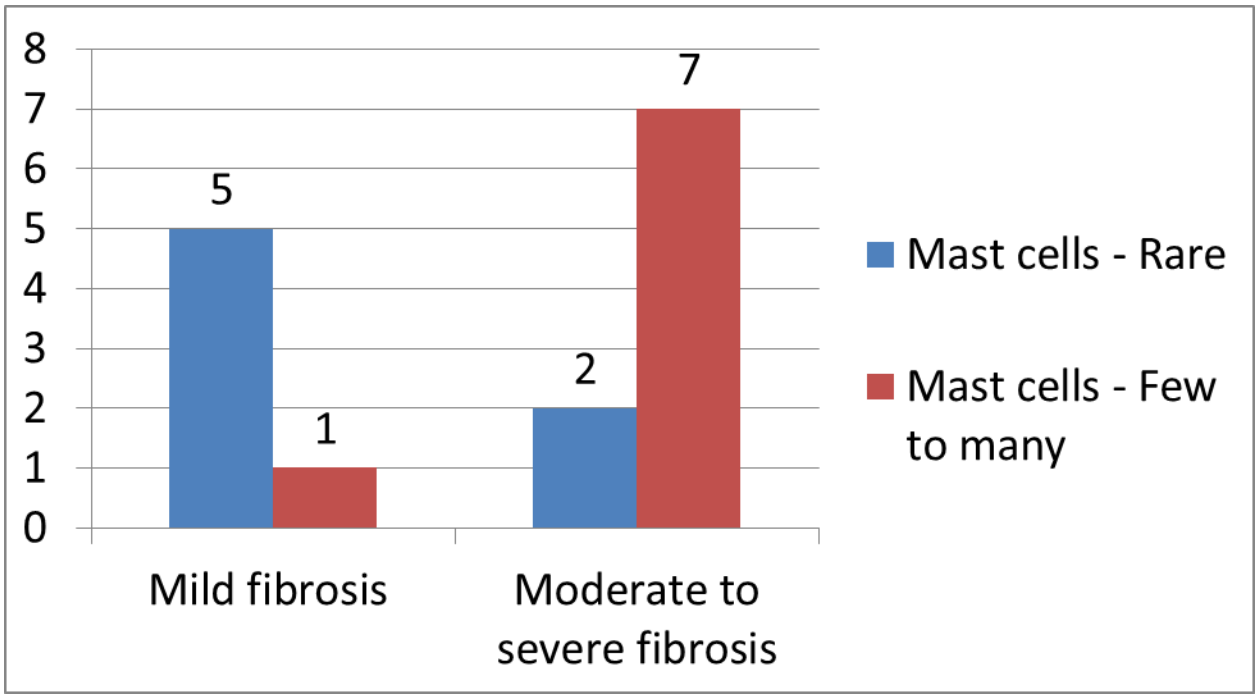


Type of Achalasia and mast cells:

In Achalasia type II, mast cells were found in 92% of the patients.



Mast cells and fibrosis: Severity of fibrosis and density of mast cells seem to have a linear relationship



Discussion

Achalasia cardia is an uncommon disease with unknown aetiology. As the specific inciting factor is unknown, the therapeutic options available for this disease is palliative.

Analysis of the clinical parameters showed a female predilection (76%). Sixty seven percent of our patients fell between 20 to 50 years of age group. Predominant symptom pre-operatively was dysphagia. Median dysphagia score was 4. Natural progression of the disease varies quite dramatically. Some patients presented as early as 4 months of onset of symptoms and some present after 15 years of onset of symtoms with recent worsening. The reason for such a diverse presentation cannot be explained. Sensory symptom like chest pain was noted only in 9% of the study population. This explains that in achalasia, both sensory and motor neurons are affected. Eighty percent of our patients were of achalasia type II with Median LES pressure of 35mmHg. Barium esophagogram revealed absent of primary peristalsis in 80% patients. Esophageal diameter could not be assessed as this was a dynamic study.

Intra-operatively, thickening of the esophageal muscle was noted in 42% of patients, probably secondary to chronic obstruction. All the patient underwent modified Heller's myotomy done by either of the two well experienced surgeons. The extent of dissection, length of myotomy, method of tissue procurement for biopsy and type of fundoplication were similar between the two surgeons. All the samples were processed by standardised technique and reported by an experienced pathologist.

In our study, we noted loss of ganglion cells in majority of our patients. Loss of ganglion cells were more pronounced with the duration of illness. Patients with duration of illness more than 5 years, ganglion cells were noted only in 12%. Overall, ganglion cells were lost in 72% of our patients. This was consistent with the studies published by Goldblum et al.

As achalasia was thought to an inflammatory disease and the ganglion cells are lost secondary to inflammation, it was of great interest to us to study the inflammatory patterns. We did not find any significant evidence of inflammation in light microscopy. However, immunohistochemistry revealed CD3 positivity lymphocytes in 8 of 14 patients (57%). This was in consistent with Villanci et al and Clark et al.

Electron microscopy did not show any evidence of on-going inflammation but there was fibrosis noted in the myentric plexus region, muscle and perimuscular and perivascular region. This is consistent with the current understanding that the primary pathology is loss of myentric ganglia. Interestingly in one of our patient, axonal degeneration of the nerve bundle involving both, myelinated nerve fibres and non-myelinated nerve fibres. A cross-section at this level with myelinated and non-myelinated fibres would be intra-esophageal preganglionic vagal nerve fibres. The changes noted could be due to the ‘dying back’ phenomenon of neuronal degeneration secondary to damage at the myentric plexus level. Casella et al of mayo clinic(58) recorded similar feature in the electron microscope and they thought it could be due to wallerian degeneration of the nerve. They also found supporting evidence or morphological changes in the brain stem and dorsal motor

nucleus. They thought achalasia is due to a central neuronal degeneration with peripheral manifestation in the esophagus rather than a primary pathology in the myentric plexus. Animal studies conducted with vagotomy have demonstrated changes mimicking achalasia but they were not consistent(59). If it is a central degenerative disorder, like Casella et al inferred, one cannot explain myentric plexitis with loss of ganglion cell and fibrosis which are the consistent features in almost all the studies done so far. Moreover, patients with post-vagotomy done for acid reduction does not present with achalasia.

We have also demonstrated eosinophil and mast cells favouring inflammation at the myentric plexus rather than central degeneration. In patients with achalasia type II, 92% of them were noted to have mast cells. Mast cells were of recent interest as they were noted to play a key role in the immunomodulation of the inflammatory diseases like inflammatory bowel disease, psoriasis, atropic dermatitis etc.(60). Most of the mast cells were noted were noted to be in granulated state. This is in line with many of the non-allergic diseases, where mast cells exhibit a phenomenon of ‘intragranular activation’ or ‘selective release’ of inflammatory mediators(60–62). In Crohns disease, mast cells in the smooth muscles region have be proven to modulate fibroblastic activity and influence hypertrophic and fibrotic response to inflammation(63).

It was interesting to see eosinophils in a few patients. Though eosinophils are commonly seen in the submucosal region of the gastro-intestinal tract, it is usually devoid in the esophagus(64). Presence of eosinophils suggests chemotactic entry to the myentric plexus region secondary to inflammation. Like,

mast cells, eosinophils are related to the inflammatory process in disease like ulcerative colitis. In fact it was thought to aid in the repair of inflammation and directly by activation of fibroblasts resulting in fibrosis of smooth muscles(65).

Fibrosis was noted in majority of our patients. In patients with duration of illness more than one year, 70 % of them revealed fibrosis. There was no difference in the degree of fibrosis or the absence of ganglion cells between achalasia type I and II. Post-operative dysphagia relief was no influenced by the degree of fibrosis as the median dysphagia score was almost equal between patients with mild fibrosis and moderate to severe fibrosis.

Women were noted to have better post-operative outcome compared with men. Patients with younger age(less than 40 years) were noted to have better dysphagia relief. Lower esophgeal sphincter pressure more than 30mmHg was a known positive predictive factor, however in our study we did not find LES pressure or the type of achalasia, influencing post-operative outcomes. 3 /21 patients had mucosal perforation. One of which had endoscopic balloon dilatation done 5 times prior to the operation. . Fundoplication did not have an impact of the dysphagia and 85% of the patient did not have symptoms of reflux disease following fundoplication.

Nasogastric tube was inserted in 17/21 patients. Patients with nasogastric tube inserted had delayed initiation of oral feeds by one day and their hospital stay extended by one day. Overall, there was delay in initiation of oral feeds and increase in the number of hospital stay compared to other centres. In our centre we do not routinely do leak test or intra-operative endoscopy which could explain the delay in onset of feeds. As many of our patients were from West-Bengal and North

eastern parts of India, they have very poor support systems outside the hospital, so we tend to keep them in hospital longer than required which could explain the increased hospital stay. Otherwise there was no wound infection or leak in any of these patients.

Therapeutically implications drawn from our study is that onset of fibrosis was noted as early as 3 months of the onset of symptoms. This probably implies that the therapeutic window is quite short even if we know the incting factors of inflammation. In view of axonal injury with preservation of myelin and shwann cells, there is a theoretical possibility of neural regeneration. Possibility of stem cell induction at the myentric plexus need evaluation. Further evaluation with animal studies could probably shed more light in the pathophysiology of the disease.

Limitations

1. Observations made cannot be validated for statistical significance as the sample size is less.
2. Post-operative dysphagia score is a subjective measure. Objective evidence of drop in lower esophageal pressure with manometry is not documented.
3. Unequal distribution of achalasia type I and type II
4. Effect of fundoplication of acid reflux can be assessed only by pH monitoring as patients with achalasia have decreased sensation.

Conclusion

1. Achalasia cardia is an inflammatory disease of the myentric plexus with early onset of fibrosis and progressive neuronal degeneration affecting myelinated and non-myelinated neurons.
2. Degree of fibrosis increases with the duration of illness.
3. Degree of fibrosis of the lower esophageal sphincter or degree of inflammation in the myentric plexus did not affect the manometric features of dysphagia or post-operative outcomes.
4. Selective inhibition of the inhibitory neurons and inciting factors are the facets of the disease which still remains an enigma.
5. Mast and eosinophils may play a key role in fibrosis.
6. Pathophysiology of this disease needs further evaluation. In view of intact myelin and shwann cells in many of the degenerated nerves, whether axonal regeneration and stem cell therapy for loss of ganglion cells will bring back the peristalsis of the esophagus is a question which can be addressed with animal studies.
7. If the molecular mechanism of mast cell and eosinophil's role is the disease could be demystified, targeted therapy can be possible by immunomodulation.
8. Positive predictive factors for dysphagia relief are younger age group and women. Type of achalasia, lower esophageal sphincter pressure, degree of fibrosis, density of ganglion cells or duration of illness have no influence on the post-operative outcomes.

9. Seven centimetre cardiomyotomy have adequate dysphagia relief.
10. Anterior fundoplication associated with modified Heller's myotomy did not influence dysphagia following the operation.
11. Insertion of nasogastric tube delays the onset of oral nutrition following surgery and prolongs the hostpital stay.

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Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

December 12, 2012

Dr. Raj Kumar J
PG Registrar
Department of General Surgery III
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**
Achalasia Cardia- An observational study on the histopathological, ultrastructural, manometric features and an analysis of short term surgical outcomes after laparoscopic hellers myotomy. Dr. Raj Kumar J, PG Registrar- Batch of 2012, Dept of General Surgery III. Paul Brand Building, Dr. Inian Samarasam, Surgery Dr. Anna Pulimood, General Pathology, Dr. Sudhakar Chandran, General Surgery Dr. Sam Varghese George, General Surgery, Dr. Sudipta Dhar Chowdhury, Gastroentrointestinal Sciences.

Ref: IRB Min. No. 8029 dated 01.10.2012

Dear Dr. Raj Kumar J,

I enclose the following documents:-

1. Institutional Review Board approval
2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
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CC: Dr. Inian Samarasam, Department of General Surgery

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Ref: IRB Min. No. 8029 dated 01.10.2012

Dear Dr. Raj Kumar J,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Achalasia Cardia- Achalasia Cardia- An observational study on the histopathological, ultrastructural, manometric features and an analysis of short term surgical outcomes after laparoscopic hellers myotomy." on October 1, 2012.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Patient Information Sheet and Consent Form (English, Hindi, Tamil and Telugu)
3. Cvs of Drs. Raj Kumar J, Anna Pulimood, Sudhakar Chandran, Inian Samarasam, Sudipta Dhar Chowdhury, Sam Varghese George.
4. A CD containing documents 1 - 3

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The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on October 1, 2012 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Priya Abraham	MBBS, MD, PhD	Professor, Virology, CMC	Clinician
Dr. Srinivasa Babu	M.Sc, M.Phil, PhD	Sr. Scientist, Neurological Sciences, CMC	Scientist
Dr. Susanne Abraham	MBBS, MD	Professor, Dermatology, Venerlogy & Leprosy, CMC.	Clinician
Dr. Paul Ravindran	PhD, Dip RP, FCCPM	Professor, Radiotherapy, CMC	
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Clinician
Dr. B.J.Prashantham	MA (Counseling), MA (Theology), Dr Min(Clinical)	Chairperson(IRB)& Director, Christian Counselling Centre	External
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External
Dr. Vathsala Sadan	M.Sc, Ph.D	Addl. Deputy Dean, College of Nursing, CMC.	Nurse
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL.	Legal Advisor, CMC.	Internal
Mr. Harikrishnan	BL	Lawyer, Vellore	External, Advocate
Mr. Sampath	BSc, BL	Advocate	External, Advocate
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, DrPH(Epid), DMHC	Retired Professor, Vellore	External, Scientist
Mr. Joseph Devaraj	BSc, BD	Chaplain, CMC	Lay person

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Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin)	Secretary IRB (EC) & Dy. Chairperson (IRB), Professor of Endocrinology & Addl. Vice Principal (Research), CMC.	Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent. And on completion of the study you are expected to submit a copy of the final report.

A sum of Rs 40,000/- (Rupees Forty thousand only) will be sanctioned for 12 months. A subsequent installments of 40,000/- each will be released at the end of the first year following the receipt of the progress report (Total amount 80,000/-).

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
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Name

Hospital number:

Address:
Phone : 1) 2)
Email :
Preoperative
Age :
Duration of symptom :
Sex : Male/Female
Height:
Weight:
BMI:

Clinical

Food impaction requiring upper endoscopy :
Weight loss:
Manometry
LES pressure:
Type of achalsia:
Esophageal diameter _6 cm:
Prior treatment with balloon dilation:
Prior treatment with botulinum toxin:
Medical treatment: calcium channel blockers – Y/N

Clinical dysphagia score:
Encircle the appropriate answer

- 0 = able to eat normal diet / no dysphagia.
- 1 = able to swallow some solid foods
- 2 = able to swallow only semi solid foods
- 3 = able to swallow liquids only
- 4 = unable to swallow anything / total dysphagia

Operative

Entirely laparoscopic procedure:
Esophagomyotomy:
Gastric extension:
fundoplication performed: Anterior/Posterior
If Not done : reason

Intra operative endoscopy:y/n
Leak test for mucosa integrity:
Intra operative mucosal injury: Y/N
IF yes * Location
- Size
- Method of repair

NG tube:
Drain:
Any other intraoperative complications :
Duration of the operation:

Postoperative:
Ng tube removed on:
Oral feeds started on:
Any evidence of leak:
Investigion:
Day:

Re- Operation : Details
Total duration of hospital stay:
Follow-up:
Dysphagia: scores
1. At discharge
2. 2 weeks post operative

3. 3 months
4. 6 months

Postoperative dilation required:
Reoperation required:
Taking antacids:

	H.NO	Address	phone number	age	sex	BMI	comorbid	duration(y	weightlos:	dysphagia	type of fo	vomiting
uttam mo	156737F		7870312345	49	M	21.6	Nil	5	2	4	3	2
lakshmi d	205047F		7870955661	27	f	18.8	nil	0.3	2	4	3	2
puja singh	018801F		9931529539	19	F	15.4	nil	0.5	2	4	2	2
sukanya d	203724F		9831414829	33	F	31.2	nil	6	2	4	2	2
Kamala Ra	241535F		8807816061	51	F	19.2	nil	0.5	1	4	1	2
urmila Pra	088445D		8752012345	25	F	20.5	nil	6	2	4	2	1
Santha	055486F		9750221761	57	F	26.2	nil	11	1	4	2	1
Jayalakshr	173141F		9441050962	34	F	25.5	no	1	2	1	3	2
sarada de	341153D		9835369321	57	F	19.7	hypertens	6	1	4	3	2
Jyothi bas	230413F		9775982254	27	F	17.6	nil	1	1	4	3	1
Shankar P	314090F		9470116730	43	M	15.3	nil	1	1	4	1	1
Dolly Mait	239272F		9804229471	56	F	24.7	nil	2	2	4	1	1
Deepika S	353553F		9543671655	32	F	20.8	nil	6	2	4	1	2
Devanai	352110F		9487401214	56	F	23.7	nil	10	1	4	1	2
Nilanjan M	333400F		9126519708	39	M	22.7	nil	15	1	4	1	2
Madhuri n	245851F		993273631	57	F	12.6	nil	1	2	4	1	2
Majkura b	413084F		8521778464	41	F	18.5	hypertens	5	2	3	1	2
Mahavir m	444572F		8102132533	50	M	15.1	nil	1	1	3	1	1
Ashok kun	451094F		9832163480	28	M	15.6	nil	3	1	4	1	2
Yazharasi	454200F		9443007387	23	F	19.8	nil	10	1	3	1	1
Lorinda	648934F		9862471728	36	F	22.8	nil	3	2	4	1	2

			Histo numb	age upto 4	sex male -	duration(y	dysphagia	2 weeks u	Duration c	LES press	Achalasia	Nerve bur	Gabglion c
EM 237	lakshmi d	205047F	19466/12	1	2	1	2	1	1	1	2	2	0
EM 277	sukanya d	203724F	24015/12	1	2	2	2	1	1	2	2	2	0
EM 278	puja singh	018801F	24016/12	1	2	1	2	2	2	2	2	2	0
EM354	Kamala Ra	241535F	32757/12	2	2	1	2	1	2	1	2	2	0
EM291	urmila Pra	088445D	25724/12	1	2	2	2	1	2	1	1	2	1
EM299	Santha	055486F	26612/12	2	2	2	2	1	2	1	1	2	0
EM321	Jayalakshr	173141F	28333/12	1	2	1	1	1	2	2	2	1	0
EM401	sarada de	341153D	39306/12	2	2	2	2	2	2	2	1	2	0
EM102	Shankar P	314090F	7386/13	2	1	1	2	2	2	1	2	0	0

pain	regurgitat	medicatio	balloon di	botulinum	upper GI s	type of ac	manometı	barium sw	Date of oe	oprative p	thicken (	t esophagoı	Gastric ext
2	2	nil	0	nil	1	High LES p	1	8.5.12		1	2	5	2
1	2	nil	0	nil	0	High LES p	1			1	2		
2	2	nil	0	nil	1	High LES p	1	17.7.12		1	1	5	2
2	2	nil	1	nil	1	High LES p	0			1	2		
2	2	nil	0	nil	1	High LES p	1	25.9.12		1	1	5	2
2	2	nil	2	nil	0	LES Length	1	31.7.12		1	2	5	2
2	2	nil	0	nil	1	Basal LES p	1	7.8.12		1	1	5	2
2	2	nil	0	nil	2	Basal LES p	1	21.8.12		1	1	5	2
1	2	nifidipine	2	nil	1	Basal LES p	1	15.11.12		1	2	5	2
2	2	nil	0	nil	1	Basal LES r	1	13.12.13		1	2	5	2
2	2	nexpro	0	nil	1	Basal LES -	1	27.2.13	lap hellers		2	5	2
2	1	ni	1	nil	1	Basal LES p	1	12.3.13	lap hellers		2	5	2
2	2	nil	0	nil	1	Basal LES p	1	12.3.13	lap hellers		1	5	2
2	2	nifidipine	0	nil	1	Basal LES p	1	19.3.13	lap hellers		2	7	3
2	1	nil	1	nil	1	Basal LES p	1	2.4.13	lap hellers		2	?	?
2	1	nil	0	nil	1	Basal LES p	1	7.5.13	lap hellers		2	6	3
2	1	nil	0	nil	1	Basal LES p	2	30.5.13	lap hellers		1	5	2
2	2	nil	0	nil	1	not done	1	4.7.13	lap hellers		1	4	3
2	2	pantop	5	nil	0		1	25.7.13	lap hellers		1	4	3
2	2		0	nil	2	Basal LES p	1	13.8.13	lap hellers		2	5	2
2	1	pantop	3	nil	0	Basal LES p	1	29.8.13	lap hellers		1	5	2

Lymphocy	Fibrosis	duration(\	Mast cells
0	1	1	1
0	2	2	1
1	2	1	3
nil	2	1	2
1	2	2	0
2	2	2	1
1	1	1	1
1	1	2	1
2	1	1	1